2001

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: K. Weddington Examiner #: 68082 Date: 8-8-02
Art Unit: 1614 Phone Number 308-4650 Serial Number: 10/030,170
Mail Box and Bldg/Room Location: CM1-2A17 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): Shigeo Takada; Yasukazu Nagato; Masahiro Murakami

Earliest Priority Filing Date: _____

Point of Contact:
Mona Smith
Technical Information Specialist
CM1 6A01
Tel. 308-3278

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

A medicament for treating diabetes

The medicament or composition comprising

1) a mixture of cyclic* and/or straight chain poly lactic acids having a condensation degree of 3 to 19.

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Date Searcher Picked Up: 8/12/02
Date Completed: 8/30/02
Searcher Prep & Review Time: 30
Clerical Prep Time: _____
Online Time: 65

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) _____
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Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN _____
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Sequence Systems _____
WWW/Internet _____
Other (specify) _____

PTO-1590 (8-01)

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FILE COVERS 1907 - 30 Aug 2002  VOL 137 ISS 10
FILE LAST UPDATED: 29 Aug 2002  (20020829/ED)

 This file contains CAS Registry Numbers for easy and accurate
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information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.

=> d stat que
L1          1460 SEA FILE=REGISTRY LACTIC ACID?/CN
L2        108950 SEA FILE=HCAPLUS L1 OR POLYLACTIC? OR ?LACTIC(W)ACID?
L3          1453 SEA FILE=HCAPLUS L2 AND DIABET?
L4        459862 SEA FILE=HCAPLUS THU/RL
L5       1181565 SEA FILE=HCAPLUS ?THERAP? OR ?PHARM? OR ?DRUG? OR ?MEDIC?
L6        400705 SEA FILE=HCAPLUS 62/SC OR 63/SC OR 64/SC
L7           417 SEA FILE=HCAPLUS L3 AND (L4 OR L5 OR L6)
L9             2 SEA FILE=HCAPLUS L7 (10W) CONDENSAT?


=> d ibib abs hitrn l9 1-2

L9   ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2001:114994  HCAPLUS
DOCUMENT NUMBER:          134:157572
TITLE:                    Polylactic acid for the treatment
                          of diabetes
INVENTOR(S):              Takada, Shigeo; Nagato, Yasuhiro; Murakami, Masahiro
PATENT ASSIGNEE(S):       Amato Pharmaceutical Products, Ltd., Japan; Tokai
                          Education Instruments Co., Ltd.
SOURCE:                   PCT Int. Appl., 23 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
```

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001010451	A1	20010215	WO 2000-IB1112	20000809
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1213021	A1	20020612	EP 2000-949844	20000809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.: JP 1999-224883 A 19990809
WO 2000-IB1112 W 20000809

AB Disclosed are **drugs** for preventing and/or treating **diabetes** or complications of **diabetes** which have a hypoglycemic effect. These **drugs** contain as the active ingredient a mixt. of cyclic and/or chain **polylactic acids** having a degree of **condensation** of from 3 to 19.

IT **26023-30-3P**, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)]
26100-51-6P, **Polylactic acid**
RL: IMF (Industrial manufacture); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(**polylactic acid** for treatment of **diabetes**
)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1982:197477 HCAPLUS
DOCUMENT NUMBER: 96:197477
TITLE: Gas chromatographic-mass spectrometric investigation of altered metabolism in **diabetic** ketoacidosis
AUTHOR(S): Niwa, Toshimitsu
CORPORATE SOURCE: Dep. Intern. Med., Nagoya Univ. Branch Hosp., Nagoya, Japan
SOURCE: JEOL News, [Ser.] Anal. Instrum. (1982), 18A(2), 66-71
CODEN: JNAIDF; ISSN: 0385-4418
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The org. acids in the urine and serum of **diabetic** patients with ketoacidosis were analyzed by gas chromatog.-mass spectrometry. In the urine approx. 50 compds. were identified. 3-Hydroxyvaleric acid, 5-hydroxyhexanoic acid, and 2-hydroxy-2-methyllevulinic acid were newly identified in the urine. These acids were undetectable in the urine after insulin **therapy** when the patients became nonketotic. The acids were not detected in the urine and serum of healthy subjects or **diabetic** patients without ketosis. 3-Hydroxyvaleric acid seems to

be formed from the **condensation** of acetyl-CoA and propionyl-CoA. 5-Hydroxyhexanoic acid seems to be formed from the .omega.-1 oxidn. and .beta.-oxidn. of nonesterified fatty acids liberated from peripheral adipose tissue. The **diabetic** patients with ketoacidosis also showed an elevated urinary excretion of lactic, 2-hydroxybutyric, 3-hydroxyisovaleric, adipic and 2,3-dideoxypentonic acids. The increased urinary excretion of **lactic acid** and 2-hydroxybutyric acid was considered to be due the elevated NADH/NAD ratio in the ketoacidosis. The increased urinary excretion of 3-hydroxyisovaleric acid seems to be due to the enhanced catabolism of leucine. The increased urinary excretion of adipic acid is due to the .omega.-oxidn. and .beta.-oxidn. of nonesterified fatty acids.

IT **50-21-5**, biological studies
RL: BIOL (Biological study)
(of urine, in **diabetic** ketoacidosis of human, gas chromatog.-mass spectrometry detn. of)

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=> fil hcaplu
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FILE COVERS 1907 - 28 Aug 2002  VOL 137 ISS 9
FILE LAST UPDATED: 26 Aug 2002  (20020826/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

CAS roles have been modified effective December 16, 2001. Please
check your SDI profiles to see if they need to be revised. For
information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.

=> d stat que
L1          1460 SEA FILE=REGISTRY LACTIC ACID?/CN
L2        107036 SEA FILE=HCAPLUS L1 OR LACTIC(W)ACID?
L3        458990 SEA FILE=HCAPLUS THU/RL
L4       1132764 SEA FILE=HCAPLUS THERAP? OR PHARM? OR MEDIC? OR DRUG?
L5        400327 SEA FILE=HCAPLUS 62/SC OR 63/SC OR 64/SC
L9          9213 SEA FILE=HCAPLUS L2 AND POLYMER?
L10           33 SEA FILE=HCAPLUS L9 AND (L3 OR L4 OR L5) AND DIABET?


=> d ibib abs hitrn l10 1-33

L10  ANSWER 1 OF 33  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:521462 HCAPLUS
DOCUMENT NUMBER:          137:88442
TITLE:                    Incensole and furanogermacrens and compounds in
                          treatment for inhibiting neoplastic lesions and
                          microorganisms
INVENTOR(S):              Shanahan-Pendergast, Elisabeth
PATENT ASSIGNEE(S):       Ire.
SOURCE:                   PCT Int. Appl., 68 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053138	A2	20020711	WO 2002-IE200001	20020102

W: AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD, UA, UG, US, VN, YU, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IE 2001-2 A 20010102
OTHER SOURCE(S): MARPAT 137:88442

AB The invention discloses the use of incensole and/or furanogermacrens, derivs. metabolites and precursors thereof in the treatment of neoplasia, particularly resistant neoplasia and immundysregulatory disorders. These compds. can be administered alone or in combination with conventional chemotherapeutic, antiviral, antiparasite agents, radiation and/or surgery. Incensole and furanogermacren and their mixt. showed antitumor activity against various human carcinomas and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.

IT **34346-01-5,** Poly(**lactic acid**-glycolic acid)
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(enteric coating of; incensole and furanogermacrens and compds. as antitumor and antimicrobial agents)

L10 ANSWER 2 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:408539 HCAPLUS
DOCUMENT NUMBER: 136:395988
TITLE: Methods and compositions for the treatment of diseases of the eye
INVENTOR(S): Bender, Hans-Markus; Haunschild, Jutta; Wiesner, Matthias; Lang, Ulrich; Friedlander, Martin
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002041910	A2	20020530	WO 2001-EP12526	20011030

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2000-124817 A 20001101
US 2000-244606P P 20001114
OTHER SOURCE(S): MARPAT 136:395988

AB Methods and compns. for prophylaxis and/or treatment of diseases of the

eye of a patient resulting angiogenesis in the eye using antagonists of the integrin receptors .alpha.v.beta.3 and /or .alpha.v.beta.5. The compns. can be nanoparticles and are administered to the eye by injection into the sclera of the eye.

IT **26023-30-3**, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)]
26100-51-6, Poly(**lactic acid**)
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(methods and compns. for the treatment of diseases of the eye)

L10 ANSWER 3 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:408471 HCAPLUS
DOCUMENT NUMBER: 136:406862
TITLE: **Polymer**-based oral nanosphere delivery systems
INVENTOR(S): Dunn, James M.
PATENT ASSIGNEE(S): PR Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002041829	A2	20020530	WO 2001-US43299	20011120
WO 2002041829	A3	20020718		

W: AU, CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

PRIORITY APPLN. INFO.: US 2000-252070P P 20001120

AB Oral nanoparticulate **pharmaceutical** formulations and related methods for controlled release delivery of chemotherapeutic and macromol. agents are described. A nanoparticulate formulation comprises a **therapeutic** agent, e.g., heparin or insulin, and a structural delivery component, a **polymer**, e.g., a lactide-glycolide copolymer, in an amt. sufficient to achieve a **therapeutic** plasma concn. and sustain the concn. over time. The formulation may further include .beta.-cyclodextrin, polyvinyl alc., and a bioadhesive adjuvant. For example, heparin nanospheres were formed from 1:1 (wt./wt.) poly(DL-lactide-co-glycolide) and heparin with the emulsion prepd. in an aq. soln. of .beta.-cyclodextrin and polyvinyl alc. Doses of 200, 400, and 600 mg/kg were administered by oral gavage in aq. bioadhesive **polymer** adjuvant soln. to rabbits. The ability to achieve significant heparin plasma levels by 2 h post dosing, and to sustain levels to 10 days was illustrated. Also, an improved insulin nanosphere formulation was prepd. using Eudragit RS 30 1000 mg, Phospholipon 90H 500 mg, .beta.-cyclodextrin 1000 mg, insulin powder 50 mg, and ethanol 50 mL. The formulation showed improved suppression of glucose levels in **diabetic** rats and extension of the effect to at least 96 h. Nanospheres may be incorporated into a tablet prepn.

IT **26023-30-3**, Resomer 202 **26811-96-1**, Poly(L-**lactic acid**)
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(prepn. of **polymer** nanospheres for oral controlled **drug** release)

L10 ANSWER 4 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:382093 HCAPLUS
DOCUMENT NUMBER: 137:114471
TITLE: Thermogelling Biodegradable Copolymer Aqueous Solutions for Injectable Protein Delivery and Tissue Engineering
AUTHOR(S): Jeong, Byeongmoon; Lee, Kyeonghee M.; Gutowska, Anna; An, Yuehuei H.
CORPORATE SOURCE: Pacific Northwest National Laboratory, Richland, WA, 99352, USA
SOURCE: Biomacromolecules (2002), 3(4), 865-868
CODEN: BOMAF6; ISSN: 1525-7797
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This paper reports on the thermogelling, biodegradable **polymer** formulations based on poly(DL-**lactic acid**-co-glycolic acid)/PEG graft copolymers for in vivo biomedical applications using animal models. The description includes **diabetic** control by sustained insulin delivery and cartilage repair by chondrocyte cell delivery. With one injection of the poly(DL-**lactic acid** -co-glycolic acid)/PEG graft copolymers insulin formulation, the blood glucose level could be controlled from 5 to 16 days in **diabetic** rats by varying the **polymer** compn. The cartilage defect was notably repaired using chondrocyte suspension in the thermogelling PLGA-g-PEG compared with a control. This report shows that thermogelling biodegradable PLGA/PEG graft copolymer system can be a promising platform for protein and cell-based **therapy**.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:368295 HCAPLUS
DOCUMENT NUMBER: 136:374851
TITLE: Delayed-release **pharmaceutical** formulations
INVENTOR(S): Mohr, Detlef; Seiffert, Tim
PATENT ASSIGNEE(S): Creative Peptides Sweden AB, Swed.; Gardner, Rebecca
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002038129	A2	20020516	WO 2001-GB4980	20011108

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,

MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10055857 A1 20020822 DE 2000-10055857 20001110
PRIORITY APPLN. INFO.: DE 2000-10055857 A 20001108

AB The invention relates to a **pharmaceutical** delayed-release formulation contg. proinsulin C-peptide and the use of the delayed-release formulations for treating complications of **diabetes**. In particular, the invention relates to delayed-release formulations in which proinsulin C-peptide is present in an absorbable matrix consisting of absorbable **polymers**. The invention also relates to microparticles which contain proinsulin C-peptide. Thus, a polyester (polylactide-polyglycolide) or **polymer** dry mix was dissolved in water and HOAc, human C-peptide was dissolved in water and HOAc and slowly dissolved in the **polymer** soln. The soln. is sprayed at 60.degree. in a spray drier at 60.degree. and dried until the microparticles can be obtained as fine flowing powders.

IT **34346-01-5P**, Resomer RG 502H
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(delayed-release **pharmaceutical** formulations)

L10 ANSWER 6 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:354080 HCAPLUS
DOCUMENT NUMBER: 136:359655
TITLE: Topical allantoin compositions for treatment of skin inflammatory diseases
INVENTOR(S): Farber, Elliott
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 52 pp., Cont.-in-part of U.S. Ser. No. 758,696.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002055531	A1	20020509	US 2001-991283	20011113
US 6281236	B1	20010828	US 1999-360095	19990723
US 2001003753	A1	20010614	US 2001-758696	20010111

PRIORITY APPLN. INFO.: US 1999-360095 A2 19990723
US 2000-570120 A2 20000512
US 2001-758696 A2 20010111

AB A method of treating a skin condition or disease characterized by ulceration, inflammation, or blistering comprises applying to the skin of a patient an allantoin-contg. compn. in a **therapeutically** effective quantity. The allantoin-contg. compn. is an oil-in-water emulsion based on an emulsifier system that includes at least one emulsifier that is either an anionic emulsifier or a nonionic emulsifier.

If the emulsifier is an anionic emulsifier, the emulsifier system can include an acidic wax such as beeswax. The nonionic emulsifiers used can include at least one nonionic emulsifier that is an ethoxylated ether or an ethoxylated ester whose carbon chain length ranges from 8 to 22 carbon atoms. Alternatively, the emulsifier system can include an acidic anionic **polymer** such as carboxypolymethylene and an anionic emulsifier. In another alternative, the emulsifier system can include the acidic anionic **polymer** and a nonionic emulsifier, or the acidic anionic **polymer** alone. In still another alternative, the emulsifier system can include cetyl alc. and stearic acid, sodium stearoyl lactylate and sodium isostearoyl lactylate, at least one polyethylene glycol ether of cetearyl alc., or a polyethylene glycol ester of stearic acid and glyceryl stearate. The compn. can include other ingredients. The pH of the compn. used in a method according to the present invention is about 3.0-6.0; preferably, a narrower pH range is used, varying with each embodiment of the compn. Among the diseases that can be treated is epidermolysis bullosa. For example, a female patient with epidermolysis bullosa was treated with the allantoin-contg. skin cream comprising 68.68% water, 1.90% 30% sodium lauryl sulfate soln., 0.15% tetrasodium EDTA, 0.12% citric acid, 10.60% lanolin oil, 4.20% cetyl alc., 2.00% stearyl alc., 1.90% beeswax, 2.00% cod liver oil, 0.50% butylated hydroxytoluene, 0.10% St. John's wort ext., 0.10% chamomile ext., 0.10% witch hazel ext., 0.10% arnica ext., 0.30% methylparaben, 0.20% propylparaben, 1.50% allantoin, and 0.20% fragrance. The cream cut the healing time for an open wound in half and actually kept blisters from spreading over larger areas.

IT **25383-99-7**, Sodium stearoyl lactylate
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(topical allantoin compns. for treatment of skin inflammatory diseases)

L10 ANSWER 7 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:354076 HCAPLUS
DOCUMENT NUMBER: 136:359654
TITLE: Compositions for delivery of a cortisol antagonist
INVENTOR(S): Marin, Per; Landh, Tomas; Ostholm, Ivan
PATENT ASSIGNEE(S): Cortendo AB, Swed.
SOURCE: U.S. Pat. Appl. Publ., 33 pp., Cont.-in-part of U.S. Ser. No. 691,688.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002055512	A1	20020509	US 2001-809979	20010316
PRIORITY APPLN. INFO.:			GB 2000-1449 A	20000121
			US 2000-691688 A2	20001018

OTHER SOURCE(S): MARPAT 136:359654
AB A compn. for controlled release of a cortisol antagonist comprises at least one release rate controlling substance together with said cortisol antagonist. The cortisol antagonist is selected from, e.g., sodium valproate, an enkephalin, an opioid, clonidine, oxytocin, mifepristone,

ketoconazole, aminogluthetimide, metyrapone, etomidate, trilostane, mitotane, phenytoin, procaine, vitamin C, a salicylate, cimetidine, lidocaine, etc. Compns. contg. a cortisol antagonist are useful for preventing or treating metabolic syndrome and symptoms and complications of **diabetes** mellitus type II. For example, ketoconazole was formulated using glycerol monooleate 70.4%, sesame oil 9.6%, and ketoconazole 20%.

IT **50-21-5D, Lactic acid,** fatty acid esters
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(compns. for delivery of cortisol antagonist)

L10 ANSWER 8 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:284636 HCAPLUS
DOCUMENT NUMBER: 136:314992
TITLE: Polypeptide compositions containing biodegradable **polymer** salts, their manufacture, and sustained-release microcapsules from the compositions
INVENTOR(S): Yamaguchi, Yoko; Takenaga, Mitsuko; Igarashi, Rie; Mizushima, Hiroshi; Ogawa, Yasuaki
PATENT ASSIGNEE(S): LTT Inst. Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002114667	A2	20020416	JP 2000-310258	20001011

AB The compns. having OD .ltoreq.2.5 at 400 nm are manufd. by mixing polypeptides with halohydrocarbon solvent soln. contg. biodegradable **polymer** multivalent metal salts and adding water-miscible org. solvents and/or H2O to the dispersion. Also claimed are sustained-release microcapsules formed from the compns., e.g. to maintain basal insulin secretion level. **Lactic acid**-glycolic acid copolymer, ZnO, Zn-free insulin powder, and CH2Cl2 were mixed and the dispersion was further mixed with glycerin to give semitransparent soln. having OD 2.4 (400 nm). The soln. was gradually added to poly(vinyl alc.) soln. contg. Zn(OAc)2 under stirring to give O/W emulsion. The emulsion was stirred at room temp. to remove CH2Cl2 to give insulin microcapsules. Release behavior of insulin from the microcapsules was tested in streptozotocin-induced **diabetic** rats.

IT **26023-30-3D,** Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)], multivalent metal salts **34346-01-5, Lactic acid**-glycolic acid copolymer
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(polypeptide compns. contg. biodegradable **polymer** salts and solvents for sustained-release microcapsules)

L10 ANSWER 9 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:158292 HCAPLUS
DOCUMENT NUMBER: 136:189324
TITLE: Composition for the delivery of live cells and methods

of use
INVENTOR(S): Costantino, Henry R.; Bonassar, Lawrence J.; Tracy, Mark A.
PATENT ASSIGNEE(S): Alkermes Controlled Therapeutics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 25 pp., Cont.-in-part of U.S. Ser. No. 612,744.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002025308	A1	20020228	US 2001-901495	20010709

PRIORITY APPLN. INFO.: US 2000-612744 A2 20000710

AB The invention relates to an improved method for administering live cells to a patient and compns. useful in the method. The compn. comprises live cells and biocompatible, biodegradable **polymer** microparticles. The cells and microparticles of the cell/microparticle compn. can be contacted immediately prior to administration, or can be contacted in culture for a specified period of time prior to administration. In the method of the invention, an effective amt. of the cell/microparticle compn. is administered to a patient in need thereof by injection to a treatment site of the patient to provide a **therapeutic** effect in the patient. The **therapeutic** effect can be, for example, the formation of new tissue at the treatment site, or the prodn. and secretion of a biol. active secretory mol. at the treatment site. The compn. comprising live cells and biocompatible, biodegradable **polymer** microparticles can be used in a method of generating new tissue in vitro. The method comprises placing the compn. in a cell culture chamber under conditions wherein a coherent mass of tissue is formed. In a particular embodiment, the culture chamber is in a specified shape which results in the generation of tissue having said shape.

IT **26023-30-3**, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)]
26100-51-6, Polylactic acid
RL: POF (Polymer in formulation); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**polymer** microparticle compn. for organ culture and delivery of live cells into the body)

L10 ANSWER 10 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:107142 HCAPLUS
DOCUMENT NUMBER: 136:156458
TITLE: **Polymer**-bound arginine deiminases for inhibiting angiogenesis
INVENTOR(S): Min, Bon Hong; Park, Myung Ok; Kim, Min Young; Park, Byung Young; Chun, Boe Gwun; Kang, Sang Wook; Moon, Chang Hee
PATENT ASSIGNEE(S): Angiolab, Inc., S. Korea
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009741	A1	20020207	WO 2001-KR1281	20010727

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: KR 2000-43454 A 20000727

AB The present invention relates to a **pharmaceutical** compn. for inhibiting angiogenesis which comprises arginine deiminase as an active ingredient, where the arginine deiminase, obtained from Mycoplasma arginini or prepd. by a genetic recombination technique, may be conjugated to an activated **polymer** to lower its immunogenicity and increase its life time. The **pharmaceutical** compn. of the present invention exhibits an excellent inhibitory activity against angiogenesis.

IT **26023-30-3D**, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)], arginine deiminase conjugates, derivs. **26100-51-6D**, Poly(**lactic acid**), arginine deiminase conjugates, derivs.
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**polymer**-bound arginine deiminases for inhibiting angiogenesis)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:763252 HCAPLUS
DOCUMENT NUMBER: 135:328097
TITLE: Process for allele discrimination by rolling circle amplification utilizing primer extension
INVENTOR(S): Abarzua, Patricio
PATENT ASSIGNEE(S): Molecular Staging, Inc., USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077390	A2	20011018	WO 2001-US11151	20010405

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,

SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002009716 A1 20020124 US 2001-827289 20010405
PRIORITY APPLN. INFO.: US 2000-194843P P 20000405

AB Disclosed are methods for allele discrimination involving the use of rolling circle amplification (RCA) coupled with primer extension and utilizing exonuclease deficient **polymerases** to distinguish matched and unmated single nucleotide sites, such as in the case of a single nucleotide polymorphism (SNP). Hybridization of the target nucleic acid to a perfectly matched primer allows primer extension, which can be monitored. Hybridization to a primer with a terminal mismatch does not result in primer extension. The method can be adapted for use with immobilized probe arrays.

IT **26023-30-3**, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)]
26100-51-6, Polylactic acid
RL: DEV (Device component use); USES (Uses)
(primer arrays immobilized on; process for allele discrimination by rolling circle amplification utilizing primer extension)

L10 ANSWER 12 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:416800 HCAPLUS
DOCUMENT NUMBER: 135:10114
TITLE: A bioabsorbable **polymeric** matrix and bioactive glass-containing antibiotic delivery system
INVENTOR(S): Tormala, Pertti; Suokas, Esa; Aro, Hannu; Koort, Jyri
PATENT ASSIGNEE(S): Bioabsorbable Concepts, Ltd., Finland
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001039812	A1	20010607	WO 2000-EP11947	20001129

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

PRIORITY APPLN. INFO.: US 1999-449667 A 19991130

AB This invention relates to bioabsorbable materials and implants used to prevent and treat infection and promote bone growth. More specifically, this invention relates to synthetic bioabsorbable **drug** delivery materials and implants comprising: (a) a synthetic bioabsorbable **polymeric** matrix; (b) an antibiotic phase dispersed into said **polymeric** matrix (1-20% antibiotic); and (c) antibacterial, bioabsorbable, bioactive glass, dispersed into said **polymeric** matrix, for the promotion of bone growth. For example, antibiotic-releasing, self-reinforced, bioabsorbable, antibacterial, osteoconductive screws for fixation of infected cancellous bone fractures and of fractures in patients with high risk of infection were prepd. by

mixing a polylactide (Resomer LR 708) with 30% of bioactive glass spheres (size distribution 50-125 .mu.m) and 6% of ciprofloxacin. The mixt. was melt extruded into a cylindrical bar (7 mm in diam.). The extruded polylactide-bioactive glass-ciprofloxacin composite rods were self-reinforced by solid state die-drawing process at 95.degree.. The self-reinforced rods (billets) were processed further to screws with the length of 40 mm and max. thread diam. of 3.5 mm by turning the threads on the rods by a lathe and by compressing the screw head to the other end of the billet in a heated mold. The advantageous effect of the screws was obsd. in the treatment of infected cancellous bone fractures in patients with high risk of infection (**diabetic** patients, patients with inferior blood circulation in extremities, patients with poor general condition, old age, alcoholism, or disease lowering the general power of resistance against infections). The effect originates from four partially overlapping phenomena: (a) strong fixation of a bone fracture or osteotomy with a strong self-reinforced screw, (b) rapid and long-lasting release of antibiotic in a concn. high enough for treatment and/or prevention of infection, (c) rapid and long-lasting dissoln. of bioactive glass and pptn. of hydroxyapatite into the surroundings of the bioactive glass particles, and (d) long-lasting antibacterial effect also originating from the dissoln. of bioactive glass.

IT **26023-30-3**, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)]
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(bioabsorbable **polymeric** matrix and bioactive glass-contg. implants for antibiotic delivery and promotion of bone growth)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:677200 HCAPLUS
DOCUMENT NUMBER: 135:50956
TITLE: Oral delivery of glucagon-like peptide-1 in a modified **polymer** preparation normalizes basal glycemia in **diabetic** db/db mice
AUTHOR(S): Joseph, J. W.; Kalitsky, J.; St-Pierre, S.; Brubaker, P. L.
CORPORATE SOURCE: Department of Physiology, University of Toronto, Toronto, ON, Can.
SOURCE: Diabetologia (2000), 43(10), 1319-1328
CODEN: DBTGAJ; ISSN: 0012-186X
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The insulinotropic hormone, glucagon-like peptide-1 (GLP-1) has been proposed for the treatment of patients with Type II (non-insulin-dependent) **diabetes** mellitus. As GLP-1 is rapidly cleaved at L-ala2 by dipeptidyl-peptidase IV, D-ala2-GLP-1 was synthesized and shown to have dipeptidyl peptidase IV resistance in vitro and enhanced bioactivity in mice during an oral glucose challenge. The actions of D-ala2-GLP-1 were, however, lost within 4 h of injection, thus necessitating frequent and invasive treatment if it is to be used **therapeutically**. To circumvent this problem, a microsphere of D-ala2-GLP-1 that could be given orally was developed. We encapsulated D-ala2-GLP-1 in poly(lactide-co-glycolide)-COOH with olive oil as a

filler, using phase inversion. The microspheres were tested in vivo by oral gavage in mice at t = 0 h followed by repeated oral glucose tolerance tests at t = 0, 4 and 8 h. The D-ala2-glucagon-like peptide-1-microspheres lowered the glycemic response to the 4 h oral glucose challenge in both normal CD1 and **diabetic** db/db mice, by 41 .+-. 12 % ($p < 0.001$) and 27 .+-. 5 % ($p < 0.001$), resp. and by 19 .+-. 11 % ($p < 0.05$) and 28 .+-. 4 % ($p < 0.001$), resp. during the 8-h test. At 4 h after the oral gavage, basal glycemia in the **diabetic** mice was reduced from 13 .+-. 1 mmol/l to 10 .+-. 1 mmol/l and was reduced further 8 h after treatment from 12 .+-. 1 mmol/l to 8 .+-. 1 mmol/l ($p < 0.05$). Giving D-ala2-GLP-1 alone orally had no effect on glycemia. The data presented here suggest that a similar microsphere prepn. could be useful in the delivery of GLP-1 to patients with Type II **diabetes**.

IT **34346-01-5, Lactic acid**-glycolic acid copolymer
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(oral microspheres of glucagon-like peptide-1 analog normalize basal glycemia in **diabetic** mice)

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:588169 HCAPLUS
DOCUMENT NUMBER: 134:36578
TITLE: **Pharmacology** of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity
AUTHOR(S): Kakuda, Thomas N.
CORPORATE SOURCE: Antiviral Pharmacology Laboratory, Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, MN, USA
SOURCE: Clinical Therapeutics (2000), 22(6), 685-708
CODEN: CLTHDG; ISSN: 0149-2918
PUBLISHER: Excerpta Medica, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 99 refs. on the function of the mitochondria and the mechanisms by which nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) cause mitochondrial toxicity. Highly active antiretroviral **therapy** (HAART) reduces rates of morbidity and mortality due to HIV disease. However, long-term treatment with these **drugs** may be assocd. with adverse effects. Nucleoside and nucleotide analogs are potent inhibitors of HIV reverse transcriptase and have become the cornerstone of HAART. Unfortunately, these **drugs** have also been shown to inhibit cellular **polymerases**, most notably mitochondrial DNA **polymerase** .gamma.. Studies of the NRTIs in enzyme assays and cell cultures demonstrate the following hierarchy of mitochondrial DNA **polymerase** .gamma. inhibition: zalcitabine .gtoreq. didanosine .gtoreq. stayudine > lamivudine > zidovudine > abacavir. In vitro investigations have also documented impairment of the mitochondrial enzymes adenylate kinase and the ADP/ATP translocator. Inhibition of DNA **polymerase** .gamma. and other mitochondrial enzymes can gradually lead to mitochondrial dysfunction and

cellular toxicity. The clin. manifestations of NRTI-induced mitochondrial toxicity resemble those of inherited mitochondrial disease (ie, hepatic steatosis, **lactic acidosis**, myopathy, nephrotoxicity, peripheral neuropathy, and pancreatitis). Fat redistribution syndrome, or HIV-assocd. lipodystrophy, is another side effect attributed in part to NRTI **therapy**. The morphol. and metabolic complications of this syndrome are similar to those of the mitochondrial disorder known as multiple sym. lipomatosis, suggesting that this too may be related to mitochondrial toxicity. The pathophysiol. of less common adverse effects of nucleoside analog **therapy**, such as **diabetes**, ototoxicity, and retinal lesions, may be related to mitochondrial dysfunction but have not been adequately studied. NRTIs can block HIV reverse transcriptase and mitochondrial DNA **polymerase** .gamma.. Inhibition of the latter enzyme is the most likely cause of the adverse effects assocd. with these **drugs**.

REFERENCE COUNT: 99 THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:472339 HCAPLUS
DOCUMENT NUMBER: 133:182867
TITLE: Enhancement of fracture repair in rats with streptozotocin-induced **diabetes** by a single injection of biodegradable microcapsules containing a bone formation stimulant, TAK-778
AUTHOR(S): Hoshino, Tetsuo; Muranishi, Hiroya; Saito, Kazuhiro; Notoya, Kohei; Makino, Haruhiko; Nagai, Hirofumi; Sohda, Takashi; Ogawa, Yasuaki
CORPORATE SOURCE: DDS Research Laboratories, Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., Osaka, 532-8686, Japan
SOURCE: Journal of Biomedical Materials Research (2000), 51(3), 299-306
CODEN: JBMRBG; ISSN: 0021-9304
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The feasibility of using microcapsules contg. a bone formation stimulant, (2R,4S)-(-)-N-(4-diethoxyphosphorylmethylphenyl)-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-benzothiepin-2-carboxamide (TAK-778) to enhance fracture repair was assessed in rats with streptozotocin-induced **diabetes**. The release profile of the microcapsules was designed to mimic a dosing regimen of multiple injections of TAK-778 soln. The soln. was injected locally every third day from day 0 (the day of operation) to day 27 according to several dosing regimens, and fracture repair was assessed at day 28. The prodn. of callus was most prominent when TAK-778 soln. was injected so that 50-75% of the total dose (5 mg TAK-778/site) was administered during the first half of the treatment period. Thus, injectable microcapsules of 30 .mu.m in mean diam. were prepd. in order to release TAK-778 over 4 wk using a biodegradable **polymer**, poly(d,l-lactic/glycolic) acid, with a copolymer ratio of 85:15 (mol/mol) and an av. mol. wt. of 14,000. A single local injection of the microcapsules markedly enhanced fracture repair, which resulted in recovery of destructive bending strength of the bone at day 28. Histol.,

the injection of TAK-778 microcapsules stimulated both fibrous and cartilaginous proliferation and periosteal ossification in the callus at day 7; bony bridge formation was obsd. at day 28. At day 56, the callus was remodeled and cortical bony union was evidenced in the microcapsule-treated fractures compared with the controls, which showed only fibrous union.

IT **34346-01-5**, Glycolic acid-**lactic acid** copolymer
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(fracture repair in animals with **diabetes** by biodegradable microcapsules contg. bone formation stimulant TAK-778)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:343346 HCAPLUS
DOCUMENT NUMBER: 133:155311
TITLE: Sustained release of recombinant human insulin-like growth factor-I for treatment of **diabetes**
AUTHOR(S): Lam, X. M.; Duenas, E. T.; Daugherty, A. L.; Levin, N.; Cleland, J. L.
CORPORATE SOURCE: Department of Pharmaceutical Research and Development, Genentech, Inc., South San Francisco, CA, 94080, USA
SOURCE: Journal of Controlled Release (2000), 67(2-3), 281-292
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recombinant human insulin-like growth factor-I (rhIGF-I) improved glycemic control and enhance insulin sensitivity in patients with a syndrome of severe insulin resistance. Therefore, the protein may be considered as an alternative **therapy** in the treatment of **diabetes** when the patients become insensitive to insulin treatment. Because the protein was administered twice/day in clin. trials, a sustained release polylactic-co-glycolic acid (PLGA) formulation for rhIGF-I with low initial burst (<20%), max. possible protein loading (15-20%) and a continuous release of 1-2 wk may provide greater patient convenience and compliance. The protein was encapsulated in PLGA for sustained release using a spray freeze-drying technique. Formulation parameters such as protein loading, **polymer** end group, and the presence of zinc carbonate were studied for their effects on in vitro release of rhIGF-I from PLGA microspheres. As the protein loading was increased, the initial burst increased. Due to the hydrophilic properties of the **polymers**, rhIGF-I encapsulated in unblocked PLGA (free acid end groups) gave a lower initial burst and a more steady-state release profile than the blocked PLGA (hydrocarbon end groups) with the same protein loading and PLGA mol. wt. At 15% wt./wt. protein loading, the addn. of 6% wt./wt. zinc carbonate as a protein release modifier to the unblocked PLGA (12 kDa) decreased the initial burst of rhIGF-I. Therefore, a formulation consisting of 15% rhIGF-I and 6% zinc carbonate in 12 kDa, unblocked 50:50 PLGA can provide the required release characteristics in vitro. Rat studies revealed that rhIGF-I in this formulation was released in vivo at a rate which was comparable to that obsd. in vitro. These studies demonstrate the potential for a sustained release, 14-day formulation for

rhIGF-I.
IT **34346-01-5**, Resomer RG502H
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(sustained release of recombinant human insulin-like growth factor-I for treatment of **diabetes**)
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 17 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:811392 HCAPLUS
DOCUMENT NUMBER: 132:45798
TITLE: Diagnostic method based on quantification of extramitochondrial DNA
INVENTOR(S): Herrnstadt, Corinna; Ghosh, Soumitra S.; Clevenger, William; Fahy, Eoin D.; Davis, Robert E.
PATENT ASSIGNEE(S): Mitokor, USA
SOURCE: PCT Int. Appl., 157 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966075	A2	19991223	WO 1999-US13426	19990614
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6218117	B1	20010417	US 1998-97889	19980615
US 2002064773	A1	20020530	US 1998-98079	19980615
CA 2330840	AA	19991223	CA 1999-2330840	19990614
AU 9948230	A1	20000105	AU 1999-48230	19990614
EP 1086249	A2	20010328	EP 1999-931800	19990614
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002518023	T2	20020625	JP 2000-554883	19990614

PRIORITY APPLN. INFO.:
US 1998-97889 A 19980615
US 1998-98079 A 19980615
US 1999-302681 A 19990430
WO 1999-US13426 W 19990614

AB Compns. and methods based on quantification of extramitochondrial DNA (exmtDNA) sequences are provided that are useful for detecting the presence of or risk for having a disease assocd. with altered mitochondrial function, and for identifying agents suitable for treating such diseases. The exmtDNA sequences have strong homol. to authentic mitochondrial DNA (mtDNA) sequences. A method for detg. the risk for or presence of a disease assocd. with altered mitochondrial function

comprises comparing a ratio r for biol. samples contg. exmtDNA and mtDNA between subjects subjects suspected of having such a disease and a second subject known to be free of such disease. The ratio r equals x/(x + y), where x is the amt. of exmtDNA in a sample and y is the amt. of mtDNA in the sample. Genomic DNA sequences are provided with high (98%) sequence homol. with human mtDNA; exmtDNA does not yield any detectable transcripts in an RT-PCR assay but is detected in assocn. with the telomere. Primer extension assays and oligonucleotide primers are provided. The exmtDNA:mtDNA ratio correlates with risk for Alzheimer's disease, particularly in combination with detn. of the ApoE genotype by primer extension assay.

L10 ANSWER 18 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:753038 HCAPLUS
DOCUMENT NUMBER: 131:356124
TITLE: Biodegradable sustained-release alginate gels
INVENTOR(S): Goldenberg, Merrill Seymour; Gu, Jian Hua
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9959549	A1	19991125	WO 1999-US10737	19990514
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6432449	B1	20020813	US 1998-80832	19980518
CA 2331446	AA	19991125	CA 1999-2331446	19990514
AU 9939939	A1	19991206	AU 1999-39939	19990514
BR 9910533	A	20010130	BR 1999-10553	19990514
EP 1079811	A1	20010307	EP 1999-923091	19990514
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002515419	T2	20020528	JP 2000-549214	19990514
NO 2000005564	A	20010118	NO 2000-5564	20001103

PRIORITY APPLN. INFO.: US 1998-80832 A 19980518
WO 1999-US10737 W 19990514

AB The present invention relates to sustained-release formulations using biodegradable alginate delayed gels or particles and methods. Leptin (100 mg/mL; 10 mM Tris HCl, pH 8.8; pH adjusted from 8.0 to 8.8 with 1M NaOH) and 6% Et alginate (15 mol%, 10 mM Tris HCl, pH 8.6) were cooled on an ice bath. Leptin (0.5 mL) was added to the 6% Et ester alginate (0.18 mL) and the mixt. stirred on an ice bath for 10-15 min; the final pH was 8.6-8.8.

To this mixt. was added a suspension of 1M CaCO3 (16 .mu.L) and the resulting suspension was mixed well. To this suspension was dropwise added, with stirring, a soln. of 0.1M ZnCl2 (100 .mu.L); water was then added to bring the vol. to 1 mL. Then a soln. of 1.68M 6-gluconolactone (56 .mu.L) was thoroughly stirred into this mixt. The final mixt. (50 mg/mL leptin, 1% Et alginate; 0.1 mL) was cast on the inside of an Eppendorf tube and left overnight at 40.degree. to gel. After overnight storage, the in vitro release was conducted in 10 mM histidine buffer, pH 7.4. The cast gel with 15 mol% degree of esterification had minimal burst and fairly const. leptin release showing 60% released in 6 days. The cast gel with 10 mol% degree of esterification had minimal burst and fairly const. leptin release showing 55% released in 6 days.

IT **113-21-3**, Lactate, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(biodegradable sustained-release alginate gels)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 19 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:659197 HCAPLUS
DOCUMENT NUMBER: 131:277016
TITLE: Keratinous protein material for wound healing
INVENTOR(S): Blanchard, Cheryl R.; Smith, Robert A.; Siller-Jackson, Arlene J.
PATENT ASSIGNEE(S): Keraplast Technologies Ltd., USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9951175	A1	19991014	WO 1999-US7702	19990408
W: CA, CN, JP, MX				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6274163	B1	20010814	US 1998-57161	19980408

PRIORITY APPLN. INFO.: US 1998-57161 A 19980408

AB A keratinous wound healing material, preferably derived from the hair of the patient or a compatible donor is described. Keratin powder can be derived from hair using processing steps including cleaning, suspending in a liq. carrier, homogenizing and removing the liq. The keratinous material may be applied to the wound in powder form or bound to **polymeric** binder and casted into a sheet. In patients with rheumatoid arthritis and **diabetes**, wounds topically treated with keratin powder were less painful and healed (epithelized) more rapidly (7 vs. 10 days) than those treated with antibiotic ointment.

IT **34346-01-5**, **Lactic acid**-glycolic acid copolymer
RL: DEV (Device component use); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**polymer**-bound keratinous protein for wound healing)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 20 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:766507 HCAPLUS
DOCUMENT NUMBER: 130:29221
TITLE: Preparation of solid porous matrixes for **pharmaceutical** uses
INVENTOR(S): Unger, Evan C.
PATENT ASSIGNEE(S): Imarx Pharmaceutical Corp., USA
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9851282	A1	19981119	WO 1998-US9570	19980512
W: AU, BR, CA, CN, JP, KR, NZ				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 2002039594	A1	20020404	US 1998-75477	19980511
AU 9873787	A1	19981208	AU 1998-73787	19980512
EP 983060	A1	20000308	EP 1998-921109	19980512
R: DE, FR, GB, IT, NL				
US 2001018072	A1	20010830	US 2001-828762	20010409

PRIORITY APPLN. INFO.: US 1997-46379P P 19970513
US 1998-75477 A 19980511
WO 1998-US9570 W 19980512

AB A solid porous matrix formed from a surfactant, a solvent, and a bioactive agent is described. Thus, amphotericin nanoparticles were prepd. by using ZrO2 beads and a surfactant. The mixt. was milled for 24 h.

IT **547-64-8**, Methyl lactate **26023-30-3**, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] **26100-51-6**, Poly(**lactic acid**)
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prepn. of solid porous matrixes for **pharmaceutical** uses)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 21 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:733777 HCAPLUS
DOCUMENT NUMBER: 130:90989
TITLE: Detection and quantification of the A3243G mutation of mitochondrial DNA by ligation detection reaction
AUTHOR(S): Nigou, M.; Parfait, B.; Clauser, E.; Olivier, J. L.
CORPORATE SOURCE: Laboratoire commun de biologie moleculaire, Hopital Saint Antoine, Paris, 75012, Fr.
SOURCE: Molecular and Cellular Probes (1998), 12(5), 273-282
CODEN: MCPRE6; ISSN: 0890-8508
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The A3243G mutation of mitochondrial DNA is assocd. to the MELAS syndrome and to transmitted forms of **diabetes** mellitus. This mutation exists in a heteroplasmic state and can be present at a minor and hardly detectable level. The aim was to design a method which could be applied to large series of samples and could provide rapid, sensitive and quant. detection of this mutation in the wild-type mitochondrial DNA background. The ability of ligation detection reaction (LDR) to satisfy these objectives was evaluated. Ligation detection reaction was performed on a model template composed of mixts. of various proportions of plasmids bearing the wild-type or mutant mitochondrial DNA sequence. Radiolabeled or fluorescent primers and the wild-type and mutant LDR products were sepd. by electrophoresis on conventional denaturing gel or on an Applied Biosystem 373. The ratios of mutant/wild-type products were consistent with the initial ratios of the plasmids in the template. The sensitivity and accuracy of the fluorescence and isotopic detection methods were similar. The detection limit of mutant DNA was 10% of total mitochondrial DNA. The percentage of mutant DNA in DNA samples extd. from leukocytes of 19 patients having the mutation at different levels, was evaluated by fluorescent or isotopic LDR. (c) 1998 Academic Press.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 22 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:721705 HCAPLUS
DOCUMENT NUMBER: 130:518
TITLE: Vanadium complexes and derivatives, their preparation, **pharmaceutical** compositions, and **therapeutic** use
INVENTOR(S): Zhang, Zaihui; Toleikis, Philip; Lemieux, Pierre
PATENT ASSIGNEE(S): Angiotech Pharmaceuticals, Inc., Can.
SOURCE: PCT Int. Appl., 111 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9849173	A1	19981105	WO 1998-CA376	19980424
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9870221	A1	19981124	AU 1998-70221	19980424
EP 984971	A1	20000315	EP 1998-916725	19980424
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1997-44793P P 19970424

WO 1998-CA376 W 19980424

OTHER SOURCE(S): MARPAT 130:518

AB Organovanadium complexes, and more specifically hydroxyoxovanadium(V), .mu.-oxo dimeric oxovanadium(V) and cis-dioxovanadium(V) complexes, are provided. The complexes may be formulated into a **pharmaceutical** compn. The complexes and/or compns. may be used in the treatment of a variety of disease states, including use as anti-proliferative and/or anti-metastatic agents and/or to treat **drug** resistant tumors and/or to methods of reducing the ability of tumors to metastasize and/or for the treatment of **diabetes**, arthritis, multiple sclerosis, diseases involving passageways of the body, and autoimmune diseases including but not limited to psoriasis and lupus.

IT **117563-96-9**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(triblock; vanadium complexes and derivs., prepn., **pharmaceutical** compns., and **therapeutic** use)

IT **26023-30-3**, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)]
26100-51-6, Polylactic acid **34346-01-5**, **Lactic acid**-glycolic acid copolymer
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(vanadium complexes and derivs., prepn., **pharmaceutical** compns., and **therapeutic** use)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 23 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:527193 HCAPLUS
DOCUMENT NUMBER: 129:166193
TITLE: **Therapeutic** treatment and prevention of infections with a bioactive material encapsulated within a biodegradable-biocompatible **polymeric** matrix
INVENTOR(S): Setterstrom, Jean A.; Van Hamont, John E.; Reid, Robert H.; Jacob, Elliot; Jeyanthi, Ramasubbu; Boedeker, Edgar C.; McQueen, Charles E.; Tice, Thomas R.; Roberts, F. Donald; Friden, Phil
PATENT ASSIGNEE(S): United States Dept. of the Army, USA; Van Hamont, John E.; et al.
SOURCE: PCT Int. Appl., 363 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9832427	A1	19980730	WO 1998-US1556	19980127

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,

FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

US 6309669	B1	20011030	US 1997-789734		19970127
AU 9863175	A1	19980818	AU 1998-63175		19980127
PRIORITY APPLN. INFO.:			US 1997-789734	A	19970127
			US 1984-590308	B1	19840316
			US 1992-867301	A2	19920410
			US 1995-446148	A2	19950522
			US 1995-446149	B2	19950522
			US 1996-590973	B2	19960124
			WO 1998-US1556	W	19980127

AB Novel burst-free, sustained release biocompatible and biodegradable microcapsules are disclosed which can be programmed to release their active core for variable durations ranging from 1-100 days in an aq. physiol. environment. The microcapsules are comprised of a core of polypeptide or other biol. active agent encapsulated in a matrix of poly(lactide/glycolide) copolymer, which may contain a **pharmaceutically** acceptable adjuvant, as a blend of upcapped free carboxyl end group and end-capped forms ranging in ratios from 100/0 to 1/99.

IT **9001-60-9**, Lactate dehydrogenase
RL: BPR (Biological process); BSU (Biological study, unclassified); DEV (Device component use); PEP (Physical, engineering or chemical process); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(of sperm; prevention of infections with a bioactive material encapsulated within a biodegradable-biocompatible **polymeric** matrix)

L10 ANSWER 24 OF 33 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:	1997:618266 HCAPLUS
DOCUMENT NUMBER:	127:259798
TITLE:	Sensors for sugars and other metal binding analytes
INVENTOR(S):	Arnold, Frances H.; Guan, Zhibin; Chen, Chao-Tsen; Chen, Guohua
PATENT ASSIGNEE(S):	California Institute of Technology, USA; Arnold, Frances H.; Guan, Zhibin; Chen, Chao-Tsen; Chen, Guohua
SOURCE:	PCT Int. Appl., 107 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9733177	A1	19970912	WO 1997-US3654	19970303

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB,

GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9720738	A1	19970922	AU 1997-20738	19970303
EP 983511	A1	20000308	EP 1997-908968	19970303
R: DE, FR, GB				
US 6063637	A	20000516	US 1997-875047	19970707
PRIORITY APPLN. INFO.:			US 1996-12756P P	19960304
			US 1995-571440 B2	19951213
			WO 1997-US3654 W	19970303

OTHER SOURCE(S): MARPAT 127:259798

AB Sensors for use in detecting the presence of sugars and other analytes (target mols.) are disclosed. The sensor is composed of a metal complex that binds to the target mol. and releases a proton or includes an exchangeable ligand which is exchanged for the target mol. during the binding interaction between the metal complex and the target mol. The result of the binding interaction is the release of a proton, hydroxide ion, or ligand species generated during the ligand exchange. Measurement of the release of proton, hydroxide ion, or other ligand species from the sensor provides an indirect indication of target mol. concn. The metal complexes may be attached to support structures to provide both anchoring and positioning of the metal ions to increase selectivity of sugar/metal complex interactions. Detection systems in which pH is used as an indication of proton or hydroxide release are disclosed, as are detection systems in which Cl- release is used. Methods for monitoring the concns. of sugars and related mols. using the metal-based sensors are also disclosed. The invention is useful for the monitoring of target mol. concns., e.g., as in monitoring glucose concn. in blood serum or s.c. tissue fluid samples of a **diabetic** patient. An example shows an implantable (subdermal) continuous glucose monitoring system using fluorescence detection and a microporous sensor material incorporating pH-sensitive fluorescent probe mols.

IT **79-33-4**, L-**Lactic acid**, analysis
RL: ANT (Analyte); ANST (Analytical study)
(sensors for sugars and other metal-binding analytes)

L10 ANSWER 25 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:501269 HCAPLUS
DOCUMENT NUMBER: 127:106334
TITLE: Interference free biosensor
INVENTOR(S): Henning, Timothy P.; Spring, Thomas G.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9722715	A1	19970626	WO 1996-US18889	19961125
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5755953	A	19980526	US 1995-563728	19951218

EP 876506 A1 19981111 EP 1996-940610 19961125
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL
JP 2000504205 T2 20000411 JP 1997-522812 19961125
PRIORITY APPLN. INFO.: US 1995-563728 19951218
WO 1996-US18889 19961125

AB Provided are microparticle forms of carbon, carbon catalysts (e.g., platinized carbon, Ru contg. carbon, etc.), and carbon-contg. elec. conductive compds. (e.g., polypyrrole, polyaniline) which are covalently linked to peroxidase. The carbon:peroxidase conjugates are suitable for use as substrates in conventional electrodes for the detn. of, e.g., glucose or lactate in blood serum. Surprisingly, the conjugates display very little sensitivity to known interfering substances (e.g., acetaminophen) and thus are suitable for use as interference-free electrodes.

IT **50-21-5, Lactic acid**, analysis
RL: ANT (Analyte); ANST (Analytical study)
(interference-free electrodes from peroxidase-carbon conjugates)

L10 ANSWER 26 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:663494 HCAPLUS
DOCUMENT NUMBER: 115:263494
TITLE: Enteric-coated **pharmaceuticals** and their preparation
INVENTOR(S): Gen, Jokyu
PATENT ASSIGNEE(S): Biomaterial Universe K. K., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 03083917	A2	19910409	JP 1989-222643	19890829

AB Enteric-coated prepns. using biodegradable aliph. polyesters as enteric coating bases and their prepn. by coating solid prepns. with enteric coating film are claimed. The enteric-coated prepns., which are completely stable in stomach, begin to decomp. in small intestine and gradually release active ingredients by drastic decompn. of the coating in large intestine. Lactose-starch tablets (300 mg/tablet) were coated with a CH_2Cl_2 soln. of poly(DL-**lactic acid**) (mol. wt. 46,000) to give enteric-coated tablets with coating amt. 10 mg/tablet. The table was not disintegrated in McIlvain buffer at pH 3.0, disintegrated in 2-3 h at pH 5.0, in 0.5-1 h at pH 7.0, and in 10-20 min at pH 8.0, vs. 1-2 h, 30-60 min, 1-2 min, and immediate disintegration for a control tablet using an aq. soln. of hydroxypropyl Me cellulose as a coating compn. Lactose-starch tablets (200 mg/tablet) contg. insulin were coated with a CH_2Cl_2 soln. of DL-**lactic acid**-glycolic acid copolymer to give enteric tablets with coating amt. 10 mg/tablet. The tablet was administered p.o. to streptozocin-induced **diabetic** rats, blood glucose level began to decrease after 5 h and the level was kept over 15 h, while a control tablet coated with hydroxypropyl cellulose showed no blood glucose-lowering effect.

IT **31587-11-8**, Poly(DL-**lactic acid**)
51063-13-9, Poly(DL-**lactic acid**), SRU
59199-59-6, Glycolic acid-DL-**lactic acid** copolymer
RL: BIOL (Biological study)
(enteric prepns. coated with, for disintegration in large intestine)

L10 ANSWER 27 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:637896 HCAPLUS
DOCUMENT NUMBER: 113:237896
TITLE: Feedback controlled-release implant for delivery of protein **drugs**
INVENTOR(S): Brown, Larry; Fischel-Ghodsian, Fariba; Langer, Robert S.
PATENT ASSIGNEE(S): Children's Medical Center Corp., USA
SOURCE: U.S., 6 pp. Cont. of U.S. Ser. No. 749,946, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4952406	A	19900828	US 1987-36158	19870403
PRIORITY APPLN. INFO.:			US 1985-749946	19850627

AB A controlled-release implant comprises a feed-back-responsive controller (enzyme), which reversibly changes the pH of the aq. microenvironment of a biol. active compd. sequestered in a fluid-penetrable, water-insol. biocompatible material, e.g. **polymer** matrix. The pH change is effected in response to a change in the concn. of the target compd. in the aq. medium surrounding the insol. material. As a result of the pH change, the aq. soly. and the release rate of the active compd. is reversibly changed. Trilysine insulin and immobilized glucose oxidase on CN-activated Sepharose beads were added to a soln. of ethylene vinyl acetate in CH2Cl2 in cold then placed at -20.degree. for 2 days, vacuum-dried at room temp. for 2 days and then 0.5 cm diam. matrixes were excised from the **polymer**. To rats with induced **diabetese** the above implants were inserted between connective tissue layers of the skin. The release of trilysin insulin to the rats' blood stream had a direct relationship to the blood glucose levels.
IT **26023-30-3**, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)]
26100-51-6, Poly(**lactic acid**
RL: BIOL (Biological study)
(implant contg. biol.-active protein and **polymer** matrix and, feedback controlled-release)

L10 ANSWER 28 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:637745 HCAPLUS
DOCUMENT NUMBER: 113:237745
TITLE: **Lactic acid** oligomer microspheres containing hydrophilic **drugs**
AUTHOR(S): Wada, R.; Hyon, S. H.; Ikada, Y.
CORPORATE SOURCE: Res. Cent. Med. Polym. Biomater., Kyoto Univ., Kyoto,

606, Japan
SOURCE: J. Pharm. Sci. (1990), 79(10), 919-24
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A new method was developed for prepn. of biodegradable **lactic acid** oligomer microspheres contg. hydrophilic **drugs**. The microspheres were obtained by removal of solvent from an oil-in-oil emulsion through evapn. The solvent used for the dispersed phase soln. was an MeCN-H2O mixt., while the continuous phase medium was cottonseed oil. Doxorubicin-HCl and insulin were successfully entrapped in the microspheres with high trapping efficiencies of 80 to 90%, and their release profiles were not accompanied with the burst effect. The release rate of the **drugs** from the microspheres was greatly affected by the initial loading of the **drugs** and the mol. wt. of the **lactic acid** oligomer.
IT **26811-96-1**, Poly(L-**lactic acid**)
RL: BIOL (Biological study)
(microspheres, prepn. of and hydrophilic **drugs** release from)

L10 ANSWER 29 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:503305 HCAPLUS
DOCUMENT NUMBER: 113:103305
TITLE: Sustained release of insulin by double-layered implant using poly(D,L-**lactic acid**)
AUTHOR(S): Yamakawa, Ichiro; Kawahara, Masahiro; Watanabe, Sumio; Miyake, Yasuo
CORPORATE SOURCE: Tsukuba Res. Lab., Eisai Co., Ltd., Tsukuba, 300-26, Japan
SOURCE: J. Pharm. Sci. (1990), 79(6), 505-9
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This report describes the advantage of double-layered implants using low mol. wt. poly(DL-**lactic acid**) in the sustained release of insulin. The double-layered implant consisted of a **polymer** matrix contg. insulin and a polylactic acid layer which was coated partially on one of the surfaces of the insulin:**polymer** matrix. The double-layered implants were compared with single-matrix implants from the standpoint of the in vitro dissoln. test and in vivo performance. In vitro release rates were controlled by changing the amt. of poly(DL-**lactic acid**) used in the **polymer** layer. In an in vivo test using **diabetic** animals, the double-layered implants provided a sustained release of insulin for 19 d, as judged by the changes in blood glucose levels and serum insulin levels after the s.c. implantation.
IT **31587-11-8**, Poly(D,L-**lactic acid**)
51063-13-9
RL: BIOL (Biological study)
(in **polymer** matrix, for sustained release insulin implants)

L10 ANSWER 30 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:13487 HCAPLUS
DOCUMENT NUMBER: 110:13487

TITLE: Insulin controlled-release microcapsules to prolong the hypoglycemic effect in **diabetic** rats
AUTHOR(S): Lin, Shan Yang; Ho, Low Tone; Chiou, Huey Lan
CORPORATE SOURCE: Dep. Med. Res., Veterans Gen. Hosp., Taipei, Taiwan
SOURCE: Biomater., Artif. Cells, Artif. Organs (1988), 16(4), 815-28
CODEN: BACOEZ; ISSN: 0890-5533
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A solvent evapn. process was used for prepg. insulin microcapsules by using biodegradable **polymers** [polylactic acid (PLA) or HP-55] and nonbiodegradable **polymers** [ethyl cellulose (EC) or ethylene-vinyl acetate coolymer (EVA)]. The release behavior of insulin microcapsules in pH 7.4 phosphate buffer soln. was studied by a continuous flow column method. Seven types of insulin microcapsules were resp. injected into the flanks of fasting-**diabetic** SD rats induced by streptozotocin. The glucose levels and insulin concns. in the blood were periodically sampled from the tail and assayed by a glucose analyzer and RIA method. Body wts. were measured twice per wk. The release rate was controllably dependent on the **polymer** used. The PLA microcapsules could maintain normal glycemia only for 5 days, whereas the PLA + 1% EVA microcapsules exhibited 2-fold the hypoglycemic effect of PLA microcapsules, but PLA + 1% EVA microcapsules treated with 4% wax extended the duration of hypoglycemic effects for 2 wk. There were no significant effects for insulin-HP-55 microcapsules. The EC microcapsules prolonged the hypoglycemic effect for 15 days, however, the EC + 1% EVA microcapsules could maintain the same effect for up 3 wk. The slower the release rate of insulin microcapsules in vitro the longer was the hypoglycemic effect of insulin microcapsules in vivo. A close relation between in vitro release behavior and in vivo hypoglycemic efficacy of insulin microcapsules was obtained.

IT **26023-30-3 26100-51-6**, Poly(**lactic acid**)
RL: BIOL (Biological study)
(controlled-release microcapsules, for insulin prolonged hypoglycemic effect)

L10 ANSWER 31 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1988:82039 HCAPLUS
DOCUMENT NUMBER: 108:82039
TITLE: Pyruvate and lactate electrochemical sensors realized with immobilized enzymes for control in artificial pancreas
AUTHOR(S): Mascini, Marco; Moscone, Danila; Pilloton, Roberto
CORPORATE SOURCE: Ist. Chim. Anal., Univ. Firenze, Florence, 50121, Italy
SOURCE: Ann. Chim. (Rome) (1987), 77(9-10), 813-24
CODEN: ANCRAI; ISSN: 0003-4592
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lactate and pyruvate sensors were obtained by immobilizing lactate oxidase and pyruvate oxidase, both obtained from Pediococcus, on **polymeric** membranes and fixing them on H2O2 electrochem. sensors. Cellulose acetate membranes with mol. cutoff of 100 was used to eliminate interference from

ascorbic acid, glutathione, etc. Lactate sensor was very stable and precise in any conditions while for pyruvate the presence of several cofactors in solns. was necessary to enhance sensitivity due to its lower concn. in blood. The sensors were coupled with an artificial pancreas for monitoring in vivo in human **diabetic** patients the fate of lactate and pyruvate other than glucose with the purpose of better dosage of insulin or any other **drug**.

IT **50-21-5, Lactic acid**, biological studies
RL: BIOL (Biological study)
(sensors for, immobilized enzymes in, in artificial pancreas)

L10 ANSWER 32 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1987:464908 HCAPLUS
DOCUMENT NUMBER: 107:64908
TITLE: Microencapsulation of living tissue and cells
INVENTOR(S): Goosen, Mattheus F. A.; O'Shea, Geraldine M.; Sun, Anthony M.
PATENT ASSIGNEE(S): Connaught Laboratories Ltd., Can.
SOURCE: Can., 26 pp.
CODEN: CAXXA4
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 1215922	A1	19861230	CA 1984-455156	19840525

AB A core material, e.g. living tissue and cells, is microencapsulated within a semipermeable membrane to form microcapsules for implantation into an animal body by (1) placing the material into an aq. soln. of a water-sol. **polymer** that can be gelled reversibly and which has free acid groups, (2) forming the soln. into droplets, (3) gelling the droplets to produce discrete shape-retaining tempory capsules, (4) forming biocompatible semipermeable membranes about the capsules by coating the capsules with a **polymer**, e.g. polylysine (mol. wt. 10,000-30,000), which contains free amino groups to cause ionic reaction with the free acid groups on the surface of the capsules, and (5) contacting these microcapsules with a biocompatible **polymeric** material which contains free neg.-charged groups capable of ionic reaction with the free amino groups in a surface layer of the microcapsule, thus forming an outer coating on the microcapsules. Islets of Langerhans (rat, etc. cell cultures) were thus microencapsulated by successive coating in Na alginate soln., extrusion-gelling into CaCl2 soln., incubation with polylysine of mol. wt. 17,000, and finally coating with Na alginate (0.03% soln).

IT **26023-30-3 26100-51-6**, Polylactic acid
RL: BIOL (Biological study)
(surface coating, for polylysine-microencapsulated animal tissue and cells)

L10 ANSWER 33 OF 33 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1986:466373 HCAPLUS
DOCUMENT NUMBER: 105:66373

TITLE: In vitro and in vivo release of insulin from poly(**lactic acid**) microbeads and pellets
AUTHOR(S): Kwong, A. K.; Chou, S.; Sun, A. M.; Sefton, M. V.; Goosen, M. F. A.
CORPORATE SOURCE: Dep. Chem. Eng. Appl. Chem., Univ. Toronto, Toronto, ON, M5S 1A4, Can.
SOURCE: J. Controlled Release (1986), 4(1), 47-62
CODEN: JCREEC
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A feasibility study was carried out in developing an alternative insulin [9004-10-8] delivery system, for the treatment of insulin-requiring adult-onset (Type II) **diabetes**, which would by-pass some of the unresolved problems assocd. with mech. insulin pumps. Insulin delivery was accomplished by the sustained release of the hormone from a biodegradable **polymer** matrix, poly(l-**lactic acid**) (PLA) [**26811-96-1**]. Injectable insulin-PLA microbeads and implantable pellets were prepd. using an emulsion/solvent evapn. technique and a solvent casting technique resp. Insulin-PLA microbeads retained between 1/10 and 3/4 of the loaded insulin. SEM anal. of the microbeads revealed surface insulin crystals and distinct channels in the PLA matrix. The 1% to 2% poly(vinyl alc.) [9002-89-5] emulsifier assisted in the formation of these surface insulin crystals. Approx. 50% of the insulin eluted from the microbeads into tris buffer within the 1st hour. The duration of action of the microbeads could be varied from a few hours to several days. Compared with the microbeads, insulin-PLA pellets showed a relatively small in vitro insulin burst effect and an almost const. insulin release rate during the 1st 13 h (7.3 U/h). A pore-release model was used to describe the mechanism of insulin release from the **polymer** matrix. In animal studies, insulin-PLA prepn., administered s.c. as a single injection of microbeads or by implantation of a pellet, lowered the blood glucose levels of chem. induced **diabetic** rats for more than 2 wk.

IT **26811-96-1**
RL: BIOL (Biological study)
(microbeads and pellets, insulin release from)

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show files
File 155:MEDLINE(R) 1966-2002/Aug W4
File   5:Biosis Previews(R) 1969-2002/Aug W4
         (c) 2002 BIOSIS
File  34:SciSearch(R) Cited Ref Sci 1990-2002/Sep W1
         (c) 2002 Inst for Sci Info
File  71:ELSEVIER BIOBASE 1994-2002/Aug W4
         (c) 2002  Elsevier Science B.V.
File  73:EMBASE 1974-2002/Aug W4
         (c) 2002 Elsevier Science B.V.
File 144:Pascal 1973-2002/Aug W4
         (c) 2002 INIST/CNRS
File 156:ToxFile 1965-2002/Aug W4
         (c) format only 2002 The Dialog Corporation
File 351:Derwent WPI 1963-2002/UD,UM &UP=200255
         (c) 2002  Thomson Derwent
File 357:Derwent Biotech Res. 1982-2002/June W1
         (c) 2002 Thomson Derwent & ISI
File 440:Current Contents Search(R) 1990-2002/Aug 30
         (c) 2002 Inst for Sci Info
File 453:Drugs of the Future 1990-2002/Jul
         (c) 2002 Prous Science
?ds

Set     Items   Description
S1        104   LACTIC?(W)ACID? (S)POLYMER? AND (DIABET? OR BLOOD(W)SUGAR -
            OR ANTIDIABET?)
S2         59   RD (unique items)
S3         36   S2 AND (THERAP? OR PHARM? OR DRUG? OR MEDIC?)
S4          0   S3 (S)CONDENSAT?
?t3/7/1-36

 3/7/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13410489   22094738   PMID: 12099835
  Thermogelling biodegradable copolymer aqueous solutions for injectable
protein delivery and tissue engineering.
  Jeong Byeongmoon; Lee Kyeonghee M; Gutowska Anna; An Yuehuei H
  Pacific Northwest National Laboratory, 902 Battelle Boulevard, P.O. Box
999, K2-44, Richland, Washington 99352, USA. bjeong@ewha.ac.kr
  Biomacromolecules (United States)  Jul-Aug 2002,  3 (4) p865-8, ISSN
1525-7797   Journal Code: 100892849
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: In Process
  This paper reports on the thermogelling, biodegradable polymer
 formulations based on poly(DL- lactic acid -co-glycolic
acid)/(poly(ethylene glycol) graft copolymers for in vivo biomedical
applications using animal models. The description includes diabetic
control by sustained insulin delivery and cartilage repair by chondrocyte
cell delivery. With one injection of the poly(DL- lactic acid
-co-glycolic acid)/(poly(ethylene glycol) graft copolymers insulin
formulation, the blood glucose level could be controlled from 5 to 16 days
in diabetic rats by varying the polymer composition. The cartilage
defect was notably repaired using chondrocyte suspension in the
thermogelling PLGA-g-PEG compared with a control. This report shows that
thermogelling biodegradable PLGA/PEG graft copolymer system can be a
promising platform for protein and cell-based therapy .
  Record Date Created: 20020708
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3/7/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10857471 20383742 PMID: 10929917
Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity.
Kakuda T N
Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis 55455, USA.
Clinical therapeutics (UNITED STATES) Jun 2000, 22 (6) p685-708, ISSN 0149-2918 Journal Code: 7706726
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
OBJECTIVE: This paper reviews the function of the mitochondria and the mechanisms by which nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) cause mitochondrial toxicity. BACKGROUND: Highly active antiretroviral therapy (HAART) reduces rates of morbidity and mortality due to HIV disease. However, long-term treatment with these drugs may be associated with adverse effects. Nucleoside and nucleotide analogues are potent inhibitors of HIV reverse transcriptase and have become the cornerstone of HAART. Unfortunately, these drugs have also been shown to inhibit cellular polymerases , most notably mitochondrial DNA polymerase gamma. RESULTS: Studies of the NRTIs in enzyme assays and cell cultures demonstrate the following hierarchy of mitochondrial DNA polymerase gamma inhibition: zalcitabine > didanosine > stavudine > lamivudine > zidovudine > abacavir. In vitro investigations have also documented impairment of the mitochondrial enzymes adenylate kinase and the adenosine diphosphate/adenosine triphosphate translocator. Inhibition of DNA polymerase gamma and other mitochondrial enzymes can gradually lead to mitochondrial dysfunction and cellular toxicity. The clinical manifestations of NRTI-induced mitochondrial toxicity resemble those of inherited mitochondrial diseases (ie, hepatic steatosis, lactic acidosis , myopathy, nephrotoxicity, peripheral neuropathy, and pancreatitis). Fat redistribution syndrome, or HIV-associated lipodystrophy, is another side effect attributed in part to NRTI therapy . The morphologic and metabolic complications of this syndrome are similar to those of the mitochondrial disorder known as multiple symmetric lipomatosis: suggesting that this too may be related to mitochondrial toxicity. The pathophysiology of less common adverse effects of nucleoside analogue therapy , such as diabetes , ototoxicity, and retinal lesions, may be related to mitochondrial dysfunction but have not been adequately studied. CONCLUSION: NRTIs can block both HIV reverse transcriptase and mitochondrial DNA polymerase gamma. Inhibition of the latter enzyme is the most likely cause of the adverse effects associated with these drugs . (99 Refs.)
Record Date Created: 20001128

3/7/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08655853 96007711 PMID: 7554321
MELAS syndrome associated with diabetes mellitus and hyperthyroidism: a case report from Taiwan.
Yang C Y; Lam H C; Lee H C; Wei Y H; Lu C C; Han T M; Tsai J L; Chuang Y H; Lee J K
Department of Medicine, National Yang-Ming University, Kaohsiung, Taiwan, Republic of China.

Clinical endocrinology (ENGLAND) Aug 1995, 43 (2) p235-9, ISSN 0300-0664 Journal Code: 0346653
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

MELAS syndrome is a form of mitochondrial myopathy with manifestations of seizure, stroke-like syndrome, lactic acidosis , ragged red muscle fibres and mitochondrial encephalopathy. The syndrome has been reported in association with a variety of endocrine and metabolic disorders including diabetes mellitus (DM), hypothalamo-pituitary hypofunction, hypothalamic growth hormone deficiency and delayed puberty. Mitochondrial DNA (mtDNA) point mutation may be the major pathological defect. However, association of MELAS syndrome with hyperthyroidism has not previously been reported. A case is reported from Taiwan of a 32-year-old woman suffering from MELAS syndrome with associated DM and hyperthyroidism. When the latter was diagnosed in April 1988, the patient underwent subtotal thyroidectomy. There was no family history of thyroid disease. Because of repeated seizures, she had computed tomography (CT) and magnetic resonance imaging (MRI) of the brain which showed focal, low-density lesions over the cerebral hemispheres. Both serum and cerebral spinal fluid lactic acid levels were elevated. Mild elevations of serum T4 and T3 and a high titre of TSH receptor antibody were still present. Hyperglycaemia was noted during hospitalization and DM confirmed by oral glucose tolerance test. Muscle biopsy showed ragged red fibres. DNA analysis showed an A-to-G transition at the 3243rd nucleotide position of the tRNA(Leu(UUR)) gene of the mtDNA from the patient. Quantitative polymerase chain reaction (PCR) and restriction analysis revealed that about 60% of the blood mtDNA was of mutant type. The patient received antithyroid drugs for hyperthyroidism, diet control for DM and anti-epileptic drugs for seizure.

Record Date Created: 19951030

3/7/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06671698 90369491 PMID: 2203895

Sustained release of insulin by double-layered implant using poly(D,L-lactic acid).

Yamakawa I; Kawahara M; Watanabe S; Miyake Y
Tsukuba Research Laboratories, Eisai Company, Ltd., Ibaraki, Japan.

Journal of pharmaceutical sciences (UNITED STATES) Jun 1990, 79 (6) p505-9, ISSN 0022-3549 Journal Code: 2985195R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

This report describes the advantage of double-layered implants using low molecular weight poly(DL- lactic acid) in the sustained release of insulin. The double-layered implant consisted of a polymer matrix containing insulin and a polylactic acid layer which was coated partially on one of the surfaces of the insulin: polymer matrix. The double-layered implants were compared with single-matrix implants from the standpoint of the in vitro dissolution test and in vivo performance. In vitro release rates were controlled by changing the amount of poly(DL- lactic acid) used in the polymer layer. In an in vivo test using diabetic animals, the double-layered implants provided a sustained release of insulin for 19 d, as judged by the changes in blood glucose levels and serum insulin levels after the subcutaneous implantation.

Record Date Created: 19901011

3/7/5 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07299301 BIOSIS NO.: 000090079188
EFFECT OF MICROENCAPSULATED ACETYLSALICYLIC ACID ON GLYCOSYLATION OF HUMAN SERUM PROTEINS IN-VITRO
AUTHOR: JURETIC D; CEPELAK I; JALSENJAK V; ZANIC-BRUBISIC T; LIPOVAC K; JALSENJAK I
AUTHOR ADDRESS: FAC. PHARM. AND BIOCHEM., UNIV. ZAGREB, 41000 ZAGREB, A KOVACICA 1, CROATIA, YUGOSLAVIA.
JOURNAL: INT J PHARM (AMST) 61 (3). 1990. 219-224. 1990
FULL JOURNAL NAME: International Journal of Pharmaceutics (Amsterdam)
CODEN: IJPHD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Acetylsalicylic acid microencapsulated in a biocompatible polymer (poly(lactic acid)) was used for the inhibition of human serum glycosylation in comparison with the free drug . At two levels of glucose and acetylsalicylic acid, the inhibition of glycosylation was markedly enhanced for the microencapsulated drug . The observed increase in inhibition was ascribed either to delayed hydrolysis of the drug or removal of glucose to microcapsules.

3/7/6 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07287250 BIOSIS NO.: 000090067137
SUSTAINED RELEASE OF INSULIN BY DOUBLE-LAYERED IMPLANT USING POLY-D L-LACTIC ACID
AUTHOR: YAMAKAWA I; KAWAHARA M; WATANABE S; MIYAKE Y
AUTHOR ADDRESS: TSUKUBA RES. LABORATORIES, EISAI COMPANY LTD., 1-3 TOKODAI 5 CHOME, TSUKUBA-SHI, IBARAKI 300-26, JAPAN.
JOURNAL: J PHARM SCI 79 (6). 1990. 505-509. 1990
FULL JOURNAL NAME: Journal of Pharmaceutical Sciences
CODEN: JPMSA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: This report describes the advantage of double-layered implants using low molecular weight poly(DL- lactic acid) in the sustained release of insulin. The double-layered implant consisted of a polymer matrix containing insulin and a polylactic acid layer which was coated partially on one of the surfaces of the insulin: polymer matrix. The double-layered implants were compared with single-matrix implants from the standpoint of the in vitro dissolution test and in vivo performance. In vitro release rates were controlled by changing the amount of poly(DL-lactic acid) used in the polymer layer. In an in vivo test using diabetic animals, the double-layered implants provided a sustained release of insulin for 19 d, as judged by the changes in blood glucose levels and serum insulin levels after the subcutaneous implantation.

3/7/7 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05225733 BIOSIS NO.: 000082066355
IN-VITRO AND IN-VIVO RELEASE OF INSULIN FROM POLYLACTIC-ACID MICROBEADS AND PELLETS
AUTHOR: KWONG A K; CHOU S; SUN A M; SEFTON M V; GOOSEN M F A
AUTHOR ADDRESS: DEP. OF CHEMICAL ENG., QUEEN'S UNIV., KINGSTON, ONT. K7L 3N6, CANADA.
JOURNAL: J CONTROLLED RELEASE 4 (1). 1986. 47-62. 1986
FULL JOURNAL NAME: Journal of Controlled Release
CODEN: JCREE
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: A feasibility study was carried out on developing an alternative insulin delivery system, for the treatment of insulin-requiring adult-onet (Type II) diabetes , which would by-pass some of the unresolved problems associated with mechanical insulin pumps. In our system, insulin delivery was accomplished by the sustained release of the hormone from a biodegradable polymer matrix, poly(l- lactic acid) (PLA). Injectable insulin-PLA microbeads and implantable pellets were prepared using an emulsion/solvent evaporation technique and a solvent casting technique respectively. Insulin-PLA microbeads between one-tenth and three-quarters of the loaded insulin. S.E.M. analysis of the microbeads revealed surface insulin crystals and distinct channels in the PLA matrix. It was found that the 1% to 2% poly(vinyl alcohol) emulsifier assisted in the formation of these surface insulin crystals. In vitro about 50% of the insulin eluted from the microbeads into tris buffer within the first hour. The duration of action of the microbeads could be varied from a few hours to several days. Compared with the microbeads, insulin-PLA pellets showed a relatively small in vitro insulin burst effect and an almost constant insulin release rate during the first 13 hours (7.3 U/h). A pore-release model was used to describe the mechanism of insulin release from the polymer matrix. In animal studies, insulin-PLA preparations, administered subcutaneously as a single injection of microbeads or by implantation of a pellet, lowered the blood glucose levels of chemically induced diabetic rats for more than two weeks.

3/7/8 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04206769 Genuine Article#: RM994 Number of References: 21
Title: MELAS SYNDROME-ASSOCIATED WITH DIABETES -MELLITUS AND HYPERTHYROIDISM - A CASE-REPORT FROM TAIWAN
Author(s): YANG CY; LAM HC; LEE HC; WEI YH; LU CC; HAN TM; TSAI JL; CHUANG YH; LEE JK
Corporate Source: VET GEN HOSP KAOHSIUNG,DEPT MED,DIV ENDOCRINOL & METAB,386 TA CHUNG 1ST RD/KAOHSIUNG 813//TAIWAN/; NATL YANG MING UNIV,DEPT MED,DIV ENDOCRINOL & METAB/KAOHSIUNG//TAIWAN/; NATL YANG MING UNIV,DEPT BIOCHEM/KAOHSIUNG//TAIWAN/; KAOHSIUNG MED COLL,SCH TECHNOL MED SCI/KAOHSIUNG//TAIWAN/; KAOHSIUNG MED COLL,DEPT NEUROL/KAOHSIUNG//TAIWAN/
Journal: CLINICAL ENDOCRINOLOGY, 1995, V43, N2 (AUG), P235-239
ISSN: 0300-0664
Language: ENGLISH Document Type: NOTE
Abstract: MELAS syndrome is a form of mitochondrial myopathy with manifestations of seizure, stroke-like syndrome, lactic acidosis , ragged red muscle fibres and mitochondrial encephalopathy, The syndrome has been reported in association with a variety of endocrine and metabolic disorders including diabetes mellitus (DM),

hypothalamo-pituitary hypofunction, hypothalamic growth hormone deficiency and delayed puberty, Mitochondrial DNA (mtDNA) point mutation may be the major pathological defect. However, association of MELAS syndrome with hyperthyroidism has not previously been reported, A case is reported from Taiwan of a 32-year-old woman suffering from MELAS syndrome with associated DM and hyperthyroidism, When the latter was diagnosed in April 1988, the patient underwent subtotal thyroidectomy. There was no family history of thyroid disease. Because of repeated seizures, she had computed tomography (CT) and magnetic resonance imaging (MRI) of the brain which showed focal, low-density lesions over the cerebral hemispheres. Both serum and cerebral spinal fluid lactic acid levels were elevated. Mild elevations of serum T4 and T3 and a high titre of TSH receptor antibody were still present. Hyperglycaemia was noted during hospitalization and DM confirmed by oral glucose tolerance test, Muscle biopsy showed ragged red fibres. DNA analysis showed an A-to-G transition at the 3243rd nucleotide position of the tRNA(Leu(UUR)) gene of the mtDNA from the patient. Quantitative polymerase chain reaction (PCR) and restriction analysis revealed that about 60% of the blood mtDNA was of mutant type. The patient received antithyroid drugs for hyperthyroidism, diet control for DM and anti-epileptic drugs for seizure.

3/7/9 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03193836 Genuine Article#: NL842 Number of References: 30
Title: A NEW VITREAL DRUG -DELIVERY SYSTEM USING AN IMPLANTABLE BIODEGRADABLE POLYMERIC DEVICE
Author(s): KIMURA H; OGURA Y; HASHIZOE M; NISHIWAKI H; HONDA Y; IKADA Y
Corporate Source: KYOTO UNIV,FAC MED,DEPT OPHTHALMOL,SAKYO KU/KYOTO 606//JAPAN/; KYOTO UNIV,FAC MED,DEPT OPHTHALMOL,SAKYO KU/KYOTO 606//JAPAN/; KYOTO UNIV,BIOMED ENGN RES CTR/KYOTO 606//JAPAN/
Journal: INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, 1994, V35, N6 (MAY) , P2815-2819
ISSN: 0146-0404
Language: ENGLISH Document Type: ARTICLE
Abstract: Purpose. The authors evaluated the feasibility of using an implantable biodegradable polymeric device to deliver drugs into the vitreous humor.

Methods. Two types of devices were prepared by compression-molding polymers of poly(DL- lactic acid) of two different molecular weights. The molecular weights of the poly(DL- lactic acid) used were 5,600 (device-1) and 9,100 (device-2). Sodium fluorescein (NaF) served as a hydrophilic drug marker. The release of the dye from the devices was studied in vitro. The intravitreal kinetics of NaF was evaluated in rabbits in vivo by fluorophotometry. The eyes were evaluated electrophysiologically and histologically to determine if there were toxic effects.

Results. Device-1 and device-2 released NaF for more than 25 and 45 days, respectively, in vitro. Detectable concentrations of NaF were present in the vitreous up to 17 days (device-1) and 28 days (device-2). Both types of devices were well tolerated, with no noted toxic effects.

Conclusions. These results suggested that this device may be a potentially effective system to deliver drugs in the vitreous.

3/7/10 (Item 1 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

01771608 2001133111
Prevalence of A-to-G mutation at nucleotide 3243 of the mitochondrial tRNASUPLeu(UUR) gene in Japanese patients with diabetes mellitus and end stage renal disease
Iwasaki N.; Babazono T.; Tsuchiya K.; Tomonaga O.; Suzuki A.; Togashi M.; Ujihara N.; Sakka Y.; Yokokawa H.; Ogata M.; Nihei H.; Iwamoto Y.
ADDRESS: N. Iwasaki, Diabetes Center, Tokyo Women's Medical University, 8-1 Kawadacho, Shinjuku-ku, Tokyo 162-8666, Japan
EMAIL: niwasaki@dmc.twmu.ac.jp
Journal: Journal of Human Genetics, 46/6 (330-334), 2001, Japan
CODEN: JHGEF
ISSN: 1434-5161
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 10

The A-to-G mutation at nucleotide 3243 of the mitochondrial tRNASUPLeu(UUR) gene (mt.3243A>G) is associated with both diabetes mellitus and myopathy, encephalopathy, lactic acidosis , and stroke-like episodes (MELAS). Recently, this mutation was found in three diabetic subjects with progressive kidney disease, suggesting that it may be a contributing factor in the development of kidney disease in patients with diabetes . The aim of this study was to evaluate the contribution of this mutation to the development of end stage renal disease (ESRD) in patients with diabetes . The study group consisted of 135 patients with diabetes and ESRD. The control group consisted of 92 non- diabetic subjects with ESRD who were receiving hemodialysis. The mt.3243A>G mutation was detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). We found the mt.3243A>G mutation in eight patients (8/135; 5.9%), all of whom were initially diagnosed with type II diabetes . Five of the eight patients were subsequently also diagnosed with MELAS. We did not find the mutation in any of the 92 non- diabetic subjects with ESRD. The prevalence of this mutation was 6.5-fold higher in patients with diabetes and ESRD than in those with diabetes alone (8/135 vs 5/550, respectively; XSUP2 = 13.704; P = 0.0002). The mt.3243A>G mutation may be a contributing genetic factor in the development of ESRD in Japanese patients with diabetes .

3/7/11 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

15595894 PASCAL No.: 02-0299244
A biodegradable injectable implant sustains systemic and ocular delivery of an aldose reductase inhibitor and ameliorates biochemical changes in a galactose-fed rat model for diabetic complications
AUKUNURU Jithan V; SUNKARA Gangadhar; AYALASOMAYAJULA Surya P; DERUITER Jack; CLARK Randall C; KOMPELLA Uday B
Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, Nebraska 68198-6025, United States; Department of Pharmacal Sciences, Auburn University, Auburn, Alabama 36849-5503, United States; Department of Ophthalmology, University of Nebraska Medical Center, Omaha, Nebraska 68198-6025, United States
Journal: Pharmaceutical research, 2002, 19 (3) 278-285
ISSN: 0724-8741 CODEN: PHREEB Availability: INIST-20257; 354000100857520100

No. of Refs.: 30 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: United States
Language: English
Purpose. To fabricate and characterize in vitro and in vivo performance of a sustained release biodegradable implant for N-4-(benzoylaminophenylsulfonyl glycine) (BAPSG), a novel aldose reductase inhibitor. Methods. The ability of BAPSG to inhibit aldosc reductase activity and glucose-induced vascular endothelial growth factor (VEGF) expression was assessed in a retinal pigment epithelial cell line (ARPE-19). A poly (DL-lactic-co-glycolic acid) implant containing 50% w/w BAPSG was fabricated and characterized for drug loading, in vitro drug release and the thermal behavior of the drug and the polymer. Implants were injected subcutaneously into a galactose-fed diabetic rat model and cataract scores, plasma and tissue drug levels, galactitol levels in the lens and the retina, glutathione levels in the plasma, lens. cornea and retina and VEGF expression in the retina were determined on or until 18 days. Results. BAPSG inhibited aldose reductase activity and reduced VEGF expression in ARPE-19 cells. Implants (1 x 4 mm), with a loading efficiency of 106 +- 7% for BAPSG, were fabricated. Upon implant fabrication, while the glass transition temperature of the polymer decreased, the melting point of the drug was not affected. In vivo drug release correlated well with in vitro release with similar 44% drug release occurring in vivo by the end of 18 days. The implant reduced galactitol accumulation, glutathione depletion, cataract scores, and VEGF expression in galactose-fed rats. Conclusions. An injectahle biodegradable implant of BAPSG sustained drug release in vitro and in vivo, and reduced galactitol accumulation. glutathione depletion, cataract scores, and VEGF expression in galactose-fed rats.

3/7/12 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal

14911230 PASCAL No.: 01-0060800
Preparation and evaluation of insulin-loaded polylactide microspheres using factorial design
YI QIAO HU; JIAN XIN GUO; LI JING WANG; RENXIANG TAN; LIANG YUAN ZHEN
Department of Biology, Nanjing University, Nanjing 210039, China; Department of Pharmaceutics, China Pharmaceutical University, Nanjing 210009, China
Journal: Drug development and industrial pharmacy, 2000, 26 (12) 1309-1313
ISSN: 0363-9045 Availability: INIST-17132; 354000094459420110
No. of Refs.: 16 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: United States
Language: English
The aim of this work was to study the influence of the concentration and molecular weight of poly (DL-lactide) (PLA) on the characteristics and in vivo biological activity of protein-loaded microspheres. At the same time, an attempt was made to achieve further optimization of the formulation. In the study, insulin was chosen as a model of protein drugs . Nine formulations of injectable insulin-loaded PLA microspheres were prepared using an emulsification and solvent evaporation process according to a factorial design. The trapping efficiency, drug loading, and the drop percentages of blood glucose levels at 24 hr and 72 hr in mice were used to evaluate the formulations. The results showed that PLA molecular weight and, especially, PLA concentration exerted influences on the

characteristics and in vivo biological activity of insulin-loaded microspheres. The drug -trapping efficiency increased with the increase of the polymer concentration. The drug loading decreased with the increase of the polymer concentration and was not obviously affected by PLA molecular weight. The drop percentage of blood glucose level at 24 hr increased with the increase of polymer concentration and molecular weight. At 72 hr, the drop percentages of blood glucose levels were slightly increased with the increase of PLA concentration and then significantly decreased after the PLA concentration was above 150 mg/ml. An optimized formulation was prepared with PLA-10k at a concentration of 200 mg/ml. The experimental values of the response variables were close to the predicted values. The results suggest that the in vivo release behavior should be taken into consideration in the design of protein-loaded PLA microspheres.

3/7/13 (Item 3 from file: 144)
DIALOG(R)File 144:Pascal

14650752 PASCAL No.: 00-0322576
Sustained release of recombinant human insulin-like growth factor-I for treatment of diabetes
LAM X M; DUENAS E T; DAUGHERTY A L; LEVIN N; CLELAND J L
Department of Pharmaceutical Research and Development, Genentech, Inc., South San Francisco, CA 94080, United States; Department of Endocrine Research, Genentech, Inc., South San Francisco, CA 94080, United States
Journal: Journal of controlled release, 2000, 67 (2-3) 281-292
ISSN: 0168-3659 CODEN: JCREEC Availability: INIST-20704; 354000088742660150
No. of Refs.: 25 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: Netherlands
Language: English
Recombinant human insulin-like growth factor-I (rhIGF-I) was found to improve glycemic control and enhance insulin sensitivity in patients with a syndrome of severe insulin resistance. Therefore, the protein may be considered as an alternative therapy in the treatment of diabetes when the patients become insensitive to insulin treatment. Because the protein was administered twice per day in the clinical trials, a sustained release polylactic-co-glycolic acid (PLGA) formulation for rhIGF-I with low initial burst (<20%), maximum possible protein loading (15-20%) and a continuous release of 1-2 weeks may provide greater patient convenience and compliance. The protein was encapsulated in PLGA for sustained release using a spray freeze-drying technique. Formulation parameters such as protein loading, polymer end group and the presence of zinc carbonate were studied for their effects on in vitro release of rhIGF-I from PLGA microspheres. As the protein loading was increased, the initial burst increased. Due to the hydrophilic properties of the polymers, rhIGF-I encapsulated in unblocked PLGA (free acid end groups) gave a lower initial burst and a more steady-state release profile than the blocked PLGA (hydrocarbon end groups) with the same protein loading and PLGA molecular weight. At 15% w/w protein loading. the addition of 6% w/w zinc carbonate as a protein release modifier to the unblocked PLGA (12 kDa) decreased the initial burst of rhIGF-I. Therefore, a formulation consisting of 15% rhIGF-I and 6% zinc carbonate in 12 kDa, unblocked 50:50 PLGA can provide the required release characteristics in vitro. Rat studies revealed that rhIGF-I in this formulation was released in vivo at a rate which was comparable to that observed in vitro. These studies demonstrate the potential for a sustained release, 14-day formulation for rhIGF-I.

3/7/14 (Item 4 from file: 144)
DIALOG(R)File 144:Pascal

12235566 PASCAL No.: 95-0459522
MELAS syndrome associated with diabetes mellitus and hyperthyroidism : a case report from Taiwan
CHWEN-YI YANG; HING-CHUNG LAM; HSIN-CHEN LEE; YAU-HUEI WEI; CHIH-CHEN LU; TIAN-MU HAN; JIN-LIAN TSAI; YEN-HWANG CHUANG; JENN-KUEN LEE
National Yang-Ming univ., dep. medicine, div. endocrinology metabolism, Kaohsiung, Taiwan
Journal: Clinical endocrinology : (Oxford), 1995, 43 (2) 235-239
ISSN: 0300-0664 CODEN: CLECAP Availability: INIST-15568; 354000053704090150
No. of Refs.: 21 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: United Kingdom
Language: English
MELAS syndrome is a form of mitochondrial myopathy with manifestations of seizure, stroke-like syndrome, lactic acidosis , ragged red muscle fibres and mitochondrial encephalopathy. The syndrome has been reported in association with a variety of endocrine and metabolic disorders including diabetes mellitus (DM), hypothalamo-pituitary hypofunction, hypothalamic growth hormone deficiency and delayed puberty. Mitochondrial DNA (mtDNA) point mutation may be the major pathological defect. However, association of MELAS syndrome with hyperthyroidism has not previously been reported. A case is reported from Taiwan of a 32-year-old woman suffering from MELAS syndrome with associated DM and hyperthyroidism. When the latter was diagnosed in April 1988, the patient underwent subtotal thyroidectomy. There was no family history of thyroid disease. Because of repeated seizures, she had computed tomography (CT) and magnetic resonance imaging (MRI) of the brain which showed focal, low-density lesions over the cerebral hemispheres. Both serum and cerebral spinal fluid lactic acid levels were elevated. Mild elevations of serum T4 and T3 and a high titre of TSH receptor antibody were still present. Hyperglycaemia was noted during hospitalization and DM confirmed by oral glucose tolerance test. Muscle biopsy showed ragged red fibres. DNA analysis showed an A-to-G transition at the 3243rd nucleotide position of the tRNA SUP L SUP e SUP u SUP (SUP U SUP U SUP R SUP) gene of the mtDNA from the patient. Quantitative polymerase chain reaction (PCR) and restriction analysis revealed that about 60% of the blood mtDNA was of mutant type. The patient received antithyroid drugs for hyperthyroidism, diet control for DM and anti-epileptic drugs for seizure.

3/7/15 (Item 1 from file: 351)
DIALOG(R)File 351:Derwent WPI

014518006
WPI Acc No: 2002-338709/200237
Administering live cells to a patient, useful for treating e.g. diabetes , involves injecting into a treatment site of the patient a composition comprising biocompatible, biodegradable polymer microparticles
Patent Assignee: ALKERMES CONTROLLED THERAPEUTICS (ALKE-N)
Inventor: BONASSAR L J; COSTANTINO H R; TRACY M A
Number of Countries: 001 Number of Patents: 001

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
US 20020025308	A1	20020228	US 2000612744	A	20000710	200237 B
			US 2001901495	A	20010709	

Priority Applications (No Type Date): US 2001901495 A 20010709; US 2000612744 A 20000710

Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
US 20020025308	A1		25	A61K-048/00	CIP of application US 2000612744

Abstract (Basic): US 20020025308 A1

NOVELTY - Administering live cells to a patient, comprising injecting into a treatment site of the patient a composition comprising biocompatible, biodegradable polymer microparticles and live cells, is new. The cells provide a therapeutic effect in the patient.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) generating a new cartilage tissue in a patient, comprising administering by injection to a treatment site of the patient a composition comprising live chondrocytes and biocompatible, biodegradable polymer microparticles;

(2) generating new internal organ tissue in a patient, comprising administering by injection to a treatment site of the patient a composition comprising live internal organ cells and biocompatible, biodegradable polymer microparticles;

(3) generating new tissue comprising placing a composition of live cells and a biocompatible, biodegradable polymer microparticles, and culturing the cells to provide a coherent mass of tissue; and

(4) a composition comprising biocompatible, biodegradable polymer microparticles and live cells.

ACTIVITY - Antidiabetic ; Antiparkinsonian; Antianemic.

No biological data is given.

MECHANISM OF ACTION - None given.

USE - The composition containing live pancreatic islet cells, which secrete insulin, is used to treat diabetes (claimed). It can also be used for cartilage regeneration (claimed), where cartilage is damaged by arthritis, trauma, or congenital deformities. The method can be used to generate new internal organ tissue (claimed). Where the cells are dopaminergic, they can be used to treat Parkinson's diseases. Other disease which can be treated include hypoparathyroidism, and anemia.

pp; 25 DwgNo 0/11

Derwent Class: A96; B04; D16; D22

International Patent Class (Main): A61K-048/00

International Patent Class (Additional): A61K-009/14; A61K-009/16

3/7/16 (Item 2 from file: 351)

DIALOG(R)File 351:Derwent WPI

014406159 **Image available**

WPI Acc No: 2002-226862/200228

Novel poly(alpha-(omega-amino alkyl) glycolic acid) useful as carrier for delivering nucleic acid or bioactive agents, such as DNA, RNA, oligonucleotides, proteins, peptides and drugs

Patent Assignee: SAMYANG CO LTD (SAMY-N)

Inventor: PARK J; SEO M

Number of Countries: 093 Number of Patents: 002

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week

WO 200197611 A1 20011227 WO 2000US25854 A 20000921 200228 B
AU 200075981 A 20020102 AU 200075981 A 20000921 200230

Priority Applications (No Type Date): US 2000595691 A 20000616
Patent Details:
Patent No Kind Lan Pg Main IPC Filing Notes
WO 200197611 A1 E 27 A01N-037/00
Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
AU 200075981 A A01N-037/00 Based on patent WO 200197611

Abstract (Basic): WO 200197611 A1

NOVELTY - Poly(alpha-(omega-amino alkyl) glycolic acid) (14) compound (I) is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a biodegradable polyester polymer of formula (I);

(2) a biodegradable, amphiphilic polyester block copolymer which comprises a polymer (II) bonded to the polymer compound of formula (I). Polymer (II) is poly(D- lactic acid), poly(L- lactic acid), poly(DL- lactic acid), poly(D-lactide), poly(L-lactide), poly(DL-lactide), polyglycolic acid, polyglycolides, poly(lactic-co-glycolic acids), poly(alpha-(4-amino butyl) lactic acid), or polycaprolactone. The polymer (I) and polymer (II) are present in a weight ratio of 20:80-80:20;

(3) a biodegradable polyester random copolymer which comprises a monomer-I of formula (III) and a monomer-II. Monomer-II is D- lactic acid , L- lactic acid , D-lactide, L-lactide, glycolic acid, glycolide, alpha-(4-amino butyl) lactic acid , or caprolactone. The monomers-I and II are present in a weight ratio of 20:80-80:20; and

(4) a composition which comprises a bioactive agent electrostatically coupled to the bio-degradable polyester polymer or copolymer.

n=10-250;

p=2-9;

R1, R2=H, 1-20C alkyl, 7-20C alkaryl, carbohydrates like lactose or galactose, polyethylene glycol or peptides

USE - As carrier for delivering nucleic acid or bioactive agents, such as DNA, RNA, oligonucleotides, proteins, peptides, drugs , antiinfectives such as antibiotics and antiviral agents; analgesics; anorexics; antihelminthics; antiarthritics; antiasthmatic agents; anticonvulsants; antidepressants; antidiabetic agents; antidiarrheals; antihistamines; antiinflammatory agents; antimigraine; antinauseants; antineoplastics; antiparkinsonism drugs ; antipruritics; antipsychotics; antipyretics; antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular preparations including potassium and calcium channel blockers, beta blockers, alpha blockers and antiarrhythmics; antihypertensives; diuretics and antidiuretics; vasodilators including general coronary, peripheral and cerebral; central nervous system stimulants; vasoconstrictors; cough and cold preparations including decongestants; hormones such as estradiol and other steroids, including corticosteroids; hypnotics; immunosuppressives; muscle relaxants; parasympatholytics; psychostimulants; sedatives and tranquilizers, and also for delivering genes, ionized and non-ionized drugs , to targeted organs of human and animal body.

ADVANTAGE - Poly(alpha-(omega-amino alkyl) glycolic acid) (I) is

nontoxic (inert during gene expression) and biodegradable within few weeks, hence easily excreted by kidney. (I) is highly positively charged, hence greatly enhances cellular binding and tissue uptake in the delivery of genes, drugs and other bioactive agents. The particle size and charge density of gene carrier is easily controllable. Dispersion containing (I) with controlled particle size has excellent organ-targeting effect. The composition is effective in delivering selected nucleic acid into hepatocytes by endocytosis mediated by galactosyl receptors on the surface of cells. The amphiphilic copolymers are dispersible in water and can therefore be used to manufacture sustained continuous release injectable formulations of drugs , such as lipophilic drugs , without the use of high temperature or extremes of pH, and, for water-soluble drugs such as polypeptides and oligonucleotides, without exposure of the drug to organic solvents during manufacture.

DESCRIPTION OF DRAWING(S) - The figure shows a schematic representation of an illustrative complex of a nucleic acid and poly(alpha-(omega-amino alkyl) glycolic acid).

Plasmid DNA (12)

Poly(alpha-(omega-amino alkyl) glycolic acid) (14)

pp; 27 DwgNo 1/4

Derwent Class: A23; A96; B04; B07; D16
International Patent Class (Main): A01N-037/00
International Patent Class (Additional): A61K-031/185; C08G-063/06; C08G-063/08; C08G-073/10

3/7/17 (Item 3 from file: 351)
DIALOG(R)File 351:Derwent WPI

014367810
WPI Acc No: 2002-188512/200224
HGF or its gene-based medicinal compositions for promoting fixation of transplanted cells in an affected site e.g. myocardial cells during severe myocardial infarction or myocardiopathy
Patent Assignee: SAWA Y (SAWA-I); SUMITOMO PHARM CO LTD (SUMU)
Inventor: MIYAGAWA S; SAWA Y; TAKETANI S
Number of Countries: 095 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200205840	A1	20020124	WO 2001JP6166	A	20010717	200224	B
AU 200171064	A	20020130	AU 200171064	A	20010717	200236	

Priority Applications (No Type Date): JP 2000217617 A 20000718
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200205840	A1	J	34	A61K-038/18	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

AU 200171064	A		A61K-038/18	Based on patent WO 200205840

Abstract (Basic): WO 200205840 A1

NOVELTY - A drug composition for promoting fixation of transplanted cells to the affected site contains hepatocyte-growth factor (HGF) or its gene as active ingredient.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the

following:
(1) medicinal compositions for inhibiting apoptosis of transplanted cells and fibrosis of the damaged myocardial site containing HGF or its gene as active ingredient;
(2) a method for promoting fixation of transplanted cells to affected site by co-administration of HGF or its gene and the cells for transplantation to the site;
(3) a method for treating ischemic or diabetic organ diseases by co-administration of HGF or its gene and the cells for transplantation to the site;
(4) the use of HGF or its gene for producing medicinal compositions for promoting fixation of transplanted cells to the affected site; and
(5) the use of HGF or its gene for producing medicinal compositions for inhibiting apoptosis of transplanted cells and fibrosis of the damaged myocardial site.
ACTIVITY - Cardiant; antidiabetic .
HGF or its gene was administered to myocardial cells for transplantation into rat myocardial infarction model, improved functions in which were shown by dimensional and contrast echocardiography, and apoptosis and fibrosis were not observed to indicate super effect of the therapy .
MECHANISM OF ACTION - None given in source material.
USE - The drug compositions are used in promoting the fixation of transplanted cells e.g. myocardial cells during severe myocardial infarction or myocardiopathy, or ischemic or diabetic organ diseases (all claimed).
ADVANTAGE - With these compositions, inhibition of apoptosis of transplanted cells and fibrosis of damaged myocardial site is possible.

pp; 34 DwgNo 0/6
Derwent Class: B04; D16
International Patent Class (Main): A61K-038/18
International Patent Class (Additional): A61K-035/34; A61K-035/39; A61K-035/76; A61K-047/34; A61K-047/42; A61K-048/00; A61P-003/10; A61P-009/10; A61P-043/00

3/7/18 (Item 4 from file: 351)
DIALOG(R)File 351:Derwent WPI

014276710
WPI Acc No: 2002-097412/200213
Producing microspheres by emulsifying a drug , in vivo degradable polymer, water miscible solvent and a homogeneous mixture containing miscible and immiscible solvents and removing solvent for polymer
Patent Assignee: TANABE SEIYAKU CO (TANA)
Inventor: KITAZAWA T; MATSUMOTO A; SUZUKI A; SUZUKI T
Number of Countries: 094 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200180835	A1	20011101	WO 2001JP3446	A	20010423	200213	B
AU 200148825	A	20011107	AU 200148825	A	20010423	200219	
JP 2002012670	A	20020115	JP 2001124457	A	20010423	200220	

Priority Applications (No Type Date): JP 2000122469 A 20000424
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200180835	A1	J	28	A61K-009/50	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA

CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS
KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO
RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR
IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
AU 200148825 A A61K-009/50 Based on patent WO 200180835
JP 2002012670 A 13 C08J-003/16

Abstract (Basic): WO 200180835 A1
NOVELTY - Preparation of microspheres comprises (i) adding a polymer solution comprising a drug , an in vivo degradable polymer, and a water miscible good solvent (solvent A) for the polymer to a homogeneous mixture comprising a solvent (solvent B) which is a poor solvent for the polymer and is miscible with solvent A and a solvent C which is a poor solvent for the polymer and is immiscible with solvent A; (ii) emulsifying the mixture to give an emulsion in which the polymer solution forms a dispersed phase and the homogeneous liquid mixture forms a continuous phase; and (iii) removing solvent A from the dispersed phase.
USE - For producing microspheres e.g. for sustained release of drugs such as antitumor agents, antidepressants, antiallergic agents, antidiabetic agents, blood circulation improvers, antilipemics, hypotensives, pain killers, bone strengthening agents, antiemetics, and vitamins.
ADVANTAGE - Give steady release over a long time e.g. 20 days.
pp; 28 DwgNo 0/5
Derwent Class: A96; B07
International Patent Class (Main): A61K-009/50; C08J-003/16
International Patent Class (Additional): A61K-009/58; A61K-047/34; B01J-013/02; B01J-013/12; C08J-003/20; C08K-005/00; C08L-101/16

3/7/19 (Item 5 from file: 351)
DIALOG(R)File 351:Derwent WPI

014181404
WPI Acc No: 2002-002101/200201
Compression-molded formulation for sustained-release of anticancer and antiarrhythmic drugs , comprises drug and particles of in-vivo degradable esterified alpha-hydroxycarboxylic acid polymer
Patent Assignee: TANABE SEIYAKU CO (TANA)
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
JP 2001187749	A	20010710	JP 200076175	A	20000317	200201	B

Priority Applications (No Type Date): JP 99295663 A 19991018
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
JP 2001187749	A		9	A61K-047/34	

Abstract (Basic): JP 2001187749 A
NOVELTY - A sustained-release compression-molded formulation (SR-CMF) comprises a drug and particles of in-vivo degradable alpha-hydroxycarboxylic acid polymer, whose terminal carboxy group is esterified by an alcohol.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for manufacture of SR-CMF, which involves compression molding a mixture containing esterified micro-particles of drug and esterified micro-particles of in-vivo degradable alpha-hydroxycarboxylic acid

polymer.
USE - For formulating sustained-release drugs such as anti-tumor physiologically active peptide, antibiotic, non-steroidal anti-inflammatory agents, antitussive and expectorants, antiulcer, antidepressant, antiallergic, cardiotonic, antiarrhythmic, vasodilater, antihypertensive, diuretic, antidiabetic , antilipaemic, anticoagulant, hemostatic, tuberculostatic, hormone, narcotic antagonist, bone resorption inhibitor, bone formation promoter and angiogenesis inhibitor.
ADVANTAGE - The compression molded formulation exhibits sustained release for a long period. The formulation can be effectively utilized for intermittent administration of vaccines and anti cancer agents. The formulation when coated with a coating film has improved storage stability, elusion control and bitterness concealment property. The manufacturing method is simple, does not require organic solvent and effectively prevents deactivation of drug .
pp; 9 DwgNo 0/5
Derwent Class: A96; B07
International Patent Class (Main): A61K-047/34
International Patent Class (Additional): A61K-009/24; A61K-009/26; C08G-063/06; C08J-003/12; C08J-005/00

3/7/20 (Item 6 from file: 351)
DIALOG(R)File 351:Derwent WPI

014172657
WPI Acc No: 2001-656885/200175
Novel composition for active embolization gene therapy , comprises a polymeric material, bioactive therapeutic factor and transfection agent
Patent Assignee: BIOSPHERE MEDICAL INC (BIOS-N)
Inventor: BOSCHETTI E; VOGEL J
Number of Countries: 095 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200172280	A2	20011004	WO 2001US9618	A	20010323	200175	B
AU 200145987	A	20011008	AU 200145987	A	20010323	200208	

Priority Applications (No Type Date): US 2000191902 P 20000324
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200172280	A2	E	77	A61K-009/00	
AU 200145987	A			A61K-009/00	Based on patent WO 200172280

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

Abstract (Basic): WO 200172280 A2
NOVELTY - Composition (I) suitable for administration to a mammal, comprises a carrier of polymeric material (PM), a bioactive factor (BF) and a transfection agent (TA).
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a pharmaceutical composition (II) suitable for embolization and gene therapy upon administration to a human, comprising (I);
(2) a kit (III) for performing embolization gene therapy , comprising a suspension of microspheres suitable for embolization and a

transfection agent for delivering genetic material to a cell; and

(3) a microparticle suitable for active embolization which comprises a polymeric material capable of embolizing a blood vessel, where the polymeric material is linked to a transfection agent which is linked to a genetic material.

ACTIVITY - Cytostatic; cardiant; antipsoriasis; nootropic; antirheumatic; antiarthritic; anti-HIV; antiarteriosclerotic; vulnerary; antidiabetic ; ophthalmological; neuroprotective; hemostatic.

MECHANISM OF ACTION - Gene therapy (claimed).

No supporting data given.

USE - (I) is useful for delivering a polynucleotide to a mammalian host, and for active embolization in a mammal host having an angiogenesis-dependent disease e.g. cancer associated with angiogenesis, or a solid tumor associated with liver, kidney, acute lymphoblastic leukemia, acute myeloid leukemia, ewing's sarcoma, gestational trophoblastic carcinoma, Hodgkin's disease, non-Hodgkin's lymphoma, Burkitt's lymphoma, diffuse large cell lymphoma, follicular mixed lymphoma, lymphoblastic lymphoma, rhabdomyosarcoma, testicular carcinoma, Wilms's tumor, anal carcinoma, bladder carcinoma, breast carcinoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, head and neck carcinoma, lung (small cell) carcinoma, multiple myeloma, follicular lymphoma, ovarian carcinoma, brain tumors (astrocytoma), cervical carcinoma, colorectal carcinoma, hepatocellular carcinoma, kaposi's sarcoma, lung (non-small-cell) carcinoma, melanoma, pancreatic carcinoma, prostate carcinoma, soft tissue sarcoma, colorectal carcinoma (stage III), osteogenic sarcoma, ovarian carcinoma (stage III), testicular carcinoma, or their combinations. (I) is also useful in gene therapy (claimed). (I) is also useful for treating non-tumorigenic angiogenesis-dependent diseases such as hypertrophic scars and keloids, proliferative diabetic retinopathy, rheumatoid arthritis, arteriovenous malformations, atherosclerotic plaques, delayed wound healing, hemophilic joints, nonunion fractures, Osier-Weber syndrome, psoriasis, pyogenic granuloma, scleroderma, tracoma, menorrhagia and vascular adhesion. Active embolization therapy is useful during surgery to remove a tumor or vascular mass of cancerous origin, and to treat or prevent metastasis. The method is also useful for treating acute bleeding, vascular abnormalities, central nervous system disorders and hypersplenism.

ADVANTAGE - (I) is suitable for safe and effective methods of embolizing gene therapy . The injected materials are not easily displaced within the tissues in which they were originally injected, thus the intended gene therapy is achieved without repeated administration or causing adverse effects to the patient. The injected materials are not readily digested, displaced or eliminated either biochemically or through the immune or lymphatic system, thus the method is more effective and longer lasting. The materials are of sufficient size to be injected through 18-26 gauge needles or 30 gauge or smaller needles, thus the method is more accurate, efficacious and less intrusive to the patient. The injected particles are flexible but are not fragile, facilitating easy injection without being broken, thus providing easy and safe injection. The injected particles are not irregularly shaped and do not clump together, also providing easy and accurate injection.

pp; 77 DwgNo 0/0

Derwent Class: A96; B04; B05; D16

International Patent Class (Main): A61K-009/00

3/7/21 (Item 7 from file: 351)

DIALOG(R)File 351:Derwent WPI
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014137308
WPI Acc No: 2001-621519/200172
Manufacture of sustained-release insulin formulation for treating diabetes , comprises dispersing preset amount of human insulin in metal salt of biodegradable polymer and molding
Patent Assignee: LLT INST CO LTD (LLTL-N)
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
JP 2001233788	A	20010828	JP 200051415	A	20000228	200172	B

Priority Applications (No Type Date): JP 200051415 A 20000228
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
JP 2001233788	A		7	A61K-038/28	

Abstract (Basic): JP 2001233788 A
NOVELTY - Sustained-release insulin formulation is manufactured by dispersing 0.5-5 weight/weight% (w/w%) of human insulin in metal salt of biodegradable polymer and molding.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for sustained-release insulin formulation obtained by the manufacturing method.
ACTIVITY - Antidiabetic .
No specific biological data given.
MECHANISM OF ACTION - None given.
USE - For treating diabetes in patients with insulin deficiency.
ADVANTAGE - The initial stage release of insulin is decreased sharply and sustained release of insulin from the formulation at fixed velocity is achieved. The sustained release insulin formulation, releases fixed quantity of insulin and efficiently maintains blood glucose level and hemostasis efficiently.
pp; 7 DwgNo 0/0
Derwent Class: A23; A96; B04
International Patent Class (Main): A61K-038/28
International Patent Class (Additional): A61K-009/10; A61K-009/52; A61K-047/30; A61K-047/34; A61P-005/48

3/7/22 (Item 8 from file: 351)
DIALOG(R)File 351:Derwent WPI
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014096983
WPI Acc No: 2001-581197/200165
Preparation of particulate drug -containing material (e.g. insulin), by mixing a drug -containing solution with an antisolvent, and encapsulating to form aerosolizable particles for inhalation
Patent Assignee: RXKINETIX INC (RXKI-N)
Inventor: ETTER J B
Number of Countries: 093 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200145731	A1	20010628	WO 2000US34436	A	20001218	200165	B
AU 200127291	A	20010703	AU 200127291	A	20001218	200165	

Priority Applications (No Type Date): US 2000604786 A 20000626; US 99469733 A 19991221

Patent Details:
Patent No Kind Lan Pg Main IPC Filing Notes
WO 200145731 A1 E 63 A61K-038/28
Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
AU 200127291 A A61K-038/28 Based on patent WO 200145731

Abstract (Basic): WO 200145731 A1

NOVELTY - Method for making a drug -containing particulate product comprises: (a) contacting a drug -containing feed solution (comprising the drug in a cosolvent system of at least 2 organic solvents) with a compressed anti-solvent fluid to precipitate drug -containing particles; and (b) separating the drug -containing particles from the anti-solvent fluid.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a particulate product for pulmonary delivery of a drug comprising a powder batch of particles including at least 1 drug . The powder batch has a tap density of 0.1-0.5 g/cm3 and is aerosolizable by an inhaler to give an aerosol having dispersed drug particles of mass median aerodynamic diameter of less than 6 microns in a carrier gas;

(2) a method for generating an aerosol for pulmonary delivery of a drug by aerosolizing drug -containing particles;

(3) a particulate product comprising a multicomponent material including a drug and a biocompatible polymer and having a degree of drug encapsulation of at least 30%. The particulate product is aerosolizable by an inhaler to give an aerosol having dispersed drug particles of mass median aerodynamic diameter of less than 6 microns; and

(4) an apparatus for generating a drug -containing aerosol for pulmonary delivery, comprising an inhaler containing particulate material, the inhaler being able to aerosolize the particles to give a drug -containing aerosol.

ACTIVITY - Antidiabetic .

MECHANISM OF ACTION - None given.

USE - Drug -containing particles (especially containing insulin) are useful for aerosolizing in an inhaler, for treating diabetic patients.

pp; 63 DwgNo 0/20

Derwent Class: A96; B04; B07
International Patent Class (Main): A61K-038/28
International Patent Class (Additional): A61K-009/12; A61K-009/14; A61K-009/16; C07K-014/62; C07K-014/64

3/7/23 (Item 9 from file: 351)
DIALOG(R)File 351:Derwent WPI

014086136
WPI Acc No: 2001-570350/200164
New, non-water soluble, film-forming bioadhesive pharmaceutical formulations disperse poorly soluble drugs in a solvent system to overcome preformulation problems
Patent Assignee: ATRIX LAB INC (ATRI-N)
Inventor: MUMPER R J; OSBORNE D W
Number of Countries: 094 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200143722	A2	20010621	WO 2000US33814	A	20001213	200164	B
AU 200120964	A	20010625	AU 200120964	A	20001213	200164	
US 6432415	B1	20020813	US 99466380	A	19991217	200255	

Priority Applications (No Type Date): US 99466380 A 19991217
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200143722	A2	E	47	A61K-009/12	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

AU 200120964	A	A61K-009/12	Based on patent WO 200143722
US 6432415	B1	A61K-007/00	

Abstract (Basic): WO 200143722 A2

NOVELTY - Non-water soluble, film-forming bioadhesive pharmaceutical formulation comprising a water-insoluble alkyl cellulose (0.1-20 weight%), a solvent system comprising a mixture of at least one volatile solvent (30-90 wt.%) and water (up to 25 wt.%), a solubilization or dispersing agent and a pharmaceutical , is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a non-water soluble, film-forming bioadhesive pharmaceutical formulation comprising:

(a) ethyl cellulose (0.1-20 wt.%);

(b) a solvent system comprising a mixture of at least one volatile solvent and water (up to 25 wt.%); and

(c) a pharmaceutical ; and

(2) a non-water soluble, film-forming bioadhesive pharmaceutical formulation comprising:

(a) ethyl cellulose (0.1-20 wt.%);

(b) ethanol (60-90 wt.%);

(c) water (up to 25 wt.%);

(d) hydroxypropylcellulose as bioerodable polymer (up to 2 wt.%);

(e) polyvinylpyrrolidone and/or polycarbophils (1-10 wt.%);

(f) imidazole (0.01-5 wt.%); and

(g) 2-amino-7-(1-methylethyl)-5-oxo-5H-(1)benzopyrano-(2,3-b)-pyridine-3-carboxylic acid (0.5-5 wt.%).

ACTIVITY - None given.

MECHANISM OF ACTION - None given.

USE - The formulations are for the effective delivery of one or more pharmaceuticals to a skin or mucosal surface (claimed).

ADVANTAGE - The formulations offer novel solutions to difficult preformulation problems of many pharmaceuticals . They can be used to deliver a wide variety of drugs . Unlike prior art bioadhesive tablets, when formulated as gel or aerosol, the composition of the invention offers controlled release kinetics which may include immediate release and it offers a very limited and almost non-existent foreign body sensation.

pp; 47 DwgNo 0/3

Derwent Class: A96; B05; B07
International Patent Class (Main): A61K-007/00; A61K-009/12
International Patent Class (Additional): A61K-009/70; A61K-047/38

3/7/24 (Item 10 from file: 351)
DIALOG(R)File 351:Derwent WPI

013991434
WPI Acc No: 2001-475649/200151
Solid composition for delivery of active agents e.g. glyburide comprises carrier optionally containing a substrate having an encapsulation coat containing hydrophilic surfactants e.g. polyoxyethylene alkylethers
Patent Assignee: LIPOCINE INC (LIPO-N)
Inventor: CHEN F; PATEL M V
Number of Countries: 094 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200137808	A1	20010531	WO 2000US32255	A	20001122	200151	B
US 6248363	B1	20010619	US 99447690	A	19991123	200151	
AU 200117981	A	20010604	AU 200117981	A	20001122	200153	

Priority Applications (No Type Date): US 99447690 A 19991123
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200137808	A1	E	106	A61K-009/14	
US 6248363	B1			A61K-009/16	
AU 200117981	A			A61K-009/14	Based on patent WO 200137808

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

Abstract (Basic): WO 200137808 A1

NOVELTY - Composition for improved delivery of active agent comprising a solid carrier optionally containing a substrate having an encapsulation coat, where the solid carrier or encapsulation coat contains at least one active agent (I) and one hydrophilic surfactant (II), is new.

ADVANTAGE - The composition is used to deliver a wide variety of active agents having improved absorption and/or biovailability. It provides coated substrate materials without the need for binders. Prior art solid carriers are limited to a few specific drugs due to difficulties in formulating appropriate drug /exicipient compositions to effectively coat the active agent onto a carrier particle. Most of prior art solid dosage forms of hydrophilic active agents exhibit poor or no absorption of the active agent. Non-solid formulations of the same are chemically instable, leak and have capsule shell incompatibility. Conventional solid dosage forms of hydrophobic active agents often exhibit slow and incomplete dissolution and subsequent absorption. They often show a high propensity for biovariability and food interactions of the active agent, resulting in restrictive compliance/labeling requirements. A comparative dissolution study was performed on 3 forms of glyburide (Ia) namely coated beads of (Ia), commercially available (Ia) and pure (Ia) bulk. 5 mg Of each form was usd for triplication dissolution runs in 500 ml of isotonic pH 7.4 phosphate buffer.The dissolutiom medium was sampled at 15, 30, 45, 60, 120 and 180 minutes. The samples were filtered and the filtrates diluted for (Ia)-specific HPLC assay. The (Ia)-coated beads showed a superior dissolution profile in the rate, extent and variability of (Ia) dissolved/released into the medium.

pp; 106 DwgNo 0/3

Derwent Class: A96; B05; B07
International Patent Class (Main): A61K-009/14; A61K-009/16
International Patent Class (Additional): A61K-009/20; A61K-009/28;

A61K-009/32; A61K-009/46; A61K-009/48; A61K-009/50; A61K-009/52; A61K-009/54; A61K-009/56; A61K-009/58

3/7/25 (Item 11 from file: 351)
DIALOG(R)File 351:Derwent WPI

013112522
WPI Acc No: 2000-284393/200025
Controlled release pharmaceutical preparations comprises core containing active agent and organic acid salt coated with (meth)acrylate film coating
Patent Assignee: ROEHM GMBH (ROHG); ROEHM GMBH & CO KG (ROHG)
Inventor: BECKERT T; LYNENSKJOLD E; PETEREIT H
Number of Countries: 088 Number of Patents: 006
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
DE 19845358	A1	20000406	DE 1045358	A	19981002	200025	B
WO 200019984	A2	20000413	WO 99EP7179	A	19990928	200026	
AU 9961974	A	20000426	AU 9961974	A	19990928	200036	
BR 9913104	A	20010508	BR 9913104	A	19990928	200129	
			WO 99EP7179	A	19990928		
EP 1117387	A2	20010725	EP 99948881	A	19990928	200143	
			WO 99EP7179	A	19990928		
KR 2001075502	A	20010809	KR 2001704111	A	20010330	200211	

Priority Applications (No Type Date): DE 1045358 A 19981002
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
DE 19845358	A1		14	A61K-009/24	
WO 200019984	A2	G		A61K-009/50	
Designated States (National): AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
AU 9961974	A			A61K-009/50	Based on patent WO 200019984
BR 9913104	A			A61K-009/50	Based on patent WO 200019984
EP 1117387	A2	G		A61K-009/50	Based on patent WO 200019984
Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
KR 2001075502	A			A61K-009/16	

Abstract (Basic): DE 19845358 A1

NOVELTY - An organic acid salt is used in active agent cores of film coated, controlled release pharmaceutical preparations.

DETAILED DESCRIPTION - A pharmaceutical preparation comprises: (a) a core containing an active agent, 2.5-97.5 wt.% (based on the core weight) of an organic acid salt and optionally a carrier and additives; and (b) a film coating comprising (meth)acrylate copolymer(s) and optionally adjuvants; with 40-100 wt.% of the copolymers comprising 93-98 wt.% radical-polymerized 1-4C alkyl esters of acrylic acid or methacrylic acid and 2-7 wt.% (meth)acrylate monomers containing a quaternary amino substituent in the alkyl group; and the copolymers being optionally in admixture with 1-60 wt.% of different (meth)acrylate copolymers comprising 85-100 wt.% radical-polymerized 1-4C alkyl esters of acrylic acid or methacrylic acid and optionally up to 15 wt.% (meth)acrylate monomers containing basic or acidic substituents in the alkyl group.

USE - The pharmaceutical preparation is especially suitable for the controlled release of analgesics, antiallergics, antiarrhythmics, antibiotics, chemotherapeutics, antidiabetics , antidotes, antiepileptics, antihypertensives, antihypotensives, anticoagulants, antimycotics, antiinflammatories, beta blockers, calcium antagonists, ACE inhibitors, broncholytics/antiasthmatics, cholinergics, corticoids, dermatologicals, diuretics, enzyme inhibitors, enzyme preparations, transport proteins, expectorants, gematrics, antiarthritics, anti-influenza agents, hormones (including sex hormones) and their inhibitors, hypnotics/sedatives, cardiac agents, lipid lowering agents, parathyroid hormone/calcium metabolism regulators, psychopharmaceuticals, spasmolytics, sympathomimetics, vitamins, wound treatment agents and cytostatics. Preferred active agents are nifedipine, diltiazem, theophylline, diclofenac Na, ketoprofen, ibuprofen, indomethacin, ambroxol, terbutaline, vincamine, propanolol, pen toxyfylline, codeine, morphine, etilefrin and carbamazepine or their salts.

ADVANTAGE - The preparation has a thin coating and gives sigmoid release curves. This release profile is only achieved in preparations known from EP 463877 and EP 436370 by virtue of the presence of a thicker coating.

pp; 14 DwgNo 0/5

Derwent Class: A14; A96; B07
International Patent Class (Main): A61K-009/16; A61K-009/24; A61K-009/50
International Patent Class (Additional): A61K-031/52

3/7/26 (Item 12 from file: 351)
DIALOG(R)File 351:Derwent WPI

012890117 **Image available**
WPI Acc No: 2000-061951/200005
Sustained-release angiotensin II antagonist composition
Patent Assignee: TAKEDA CHEM IND LTD (TAKE)
Inventor: IGARI Y; INADA Y; KAMEI S; SAIKAWA A
Number of Countries: 085 Number of Patents: 013
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9944590	A1	19990910	WO 99JP1011	A	19990303	200005	B
JP 11315034	A	19991116	JP 9955043	A	19990303	200005	
AU 9927451	A	19990920	AU 9927451	A	19990303	200007	
NO 200004350	A	20001003	WO 99JP1011	A	19990303	200058	
			NO 20004350	A	20000901		
CZ 200003164	A3	20001115	WO 99JP1011	A	19990303	200064	
			CZ 20003164	A	19990303		
EP 1058541	A1	20001213	EP 99907846	A	19990303	200066	
			WO 99JP1011	A	19990303		
BR 9908474	A	20001205	BR 998474	A	19990303	200101	
			WO 99JP1011	A	19990303		
ZA 9901706	A	20001227	ZA 991706	A	19990303	200103	
SK 200001190	A3	20010212	WO 99JP1011	A	19990303	200112	
			SK 20001190	A	19990303		
CN 1291888	A	20010418	CN 99803444	A	19990303	200141	
MX 2000008171	A1	20010401	MX 20008171	A	20000821	200171	
HU 200101439	A2	20011029	WO 99JP1011	A	19990303	200175	
			HU 20011439	A	19990303		
KR 2001086245	A	20010910	KR 2000708919	A	20000814	200219	

Priority Applications (No Type Date): JP 9852366 A 19980304
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9944590	A1	E	67	A61K-009/16	
Designated States (National): AL AM AU AZ BA BB BG BR BY CA CN CU CZ EE GD GE HR HU ID IL IN IS JP KG KR KZ LC LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK SL TJ TM TR TT UA US UZ VN YU					
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
JP 11315034	A		22	A61K-047/34	
AU 9927451	A				Based on patent WO 9944590
NO 200004350	A			A61K-009/22	
CZ 200003164	A3			A61K-009/16	Based on patent WO 9944590
EP 1058541	A1	E		A61K-009/16	Based on patent WO 9944590
Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
BR 9908474	A			A61K-009/16	Based on patent WO 9944590
ZA 9901706	A		63	A61K-000/00	
SK 200001190	A3			A61K-009/16	
CN 1291888	A			A61K-009/16	
MX 2000008171	A1			A61K-031/00	
HU 200101439	A2			A61K-009/16	Based on patent WO 9944590
KR 2001086245	A			A61K-047/30	

Abstract (Basic): WO 9944590 A1

NOVELTY - Sustained-release composition comprising a compound (I) having angiotensin II antagonistic activity (excluding 2-ethyl-5,7-dimethyl-3-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)imidazo(4,5-b)pyridine and its salt) or its prodrug or salt and a biodegradable polymer (II), is new.

ACTIVITY - Cardiovascular

MECHANISM OF ACTION - Angiotensin II antagonists

USE - For treatment or prevention of circulatory diseases, hypertension, hypercardia, cardiac insufficiency, myocardial infarction, cerebral apoplexy, ischemic peripheral circulation disturbances, myocardial ischemia, vein insufficiency, progressive cardiac insufficiency after myocardial infarction, diabetic complication, diabetic retinopathy, diabetic nephropathy, nephritis, glomerulonephritis, arteriosclerosis, angiohypertrophy, vascular hypertrophy or obstruction after intervention, vascular reobstruction after bypass surgery, hyperaldosteronism glomerulosclerosis, renal insufficiency, glaucoma, intraocular high tension hyperlipemia, angina pectoris, aneurysm, coronary arteriosclerosis, cerebral arteriosclerosis, peripheral arteriosclerosis, thrombosis, disease of central nervous system, Alzheimer's disease, deficiency of memory, depression, amnesia, senile dementia, sensory disturbances, multiple system organ failure, disease due to endothelial dysfunction or scleroderma or the prevention or amelioration of anxiety neurosis, catatonia, indisposition or dyspeptic symptoms (claimed). The compounds are used to maintain circadian rhythm of blood pressure for a long time.

ADVANTAGE - The composition is stable and active.

pp; 67 DwgNo 0/0

Derwent Class: A23; A96; B02

International Patent Class (Main): A61K-000/00; A61K-009/16; A61K-009/22; A61K-031/00; A61K-047/30; A61K-047/34

International Patent Class (Additional): A61K-009/52; A61K-031/415; A61K-031/4184; A61K-045/00; A61K-047/02; A61P-009/00; A61P-009/12; A61P-025/00; A61P-039/00; C09K-011/08; H01J-031/15

3/7/27 (Item 13 from file: 351)

DIALOG(R)File 351:Derwent WPI

012804508
WPI Acc No: 1999-610738/199952
Production of a sustained release preparation for delivery of polypeptides
Patent Assignee: TAKEDA CHEM IND LTD (TAKE)
Inventor: IWASA S; MISAKI M; YAMAGATA Y
Number of Countries: 086 Number of Patents: 008
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9948519	A1	19990930	WO 99JP1359	A	19990318	199952	B
JP 11322631	A	19991124	JP 9974793	A	19990319	200006	
AU 9928533	A	19991018	AU 9928533	A	19990318	200009	
EP 1061948	A1	20001227	EP 99909234	A	19990318	200102	
			WO 99JP1359	A	19990318		
CN 1301172	A	20010627	CN 99806413	A	19990318	200158	
KR 2001042079	A	20010525	KR 2000710431	A	20000920	200168	
ZA 200004597	A	20020227	ZA 20004597	A	20000901	200223	
AU 744354	B	20020221	AU 9928533	A	19990318	200223	

Priority Applications (No Type Date): JP 9871853 A 19980320
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9948519	A1	E	53	A61K-038/27	
Designated States (National): AE AL AM AU AZ BA BB BG BR BY CA CN CU CZ EE GD GE HR HU ID IL IN IS JP KG KR KZ LC LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK SL TJ TM TR TT UA US UZ VN YU ZA					
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
JP 11322631	A		16	A61K-038/27	
AU 9928533	A				Based on patent WO 9948519
EP 1061948	A1	E		A61K-038/27	Based on patent WO 9948519
Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
CN 1301172	A			A61K-038/27	
KR 2001042079	A			A61K-038/27	
ZA 200004597	A		61	A61K-000/00	
AU 744354	B			A61K-038/27	Previous Publ. patent AU 9928533 Based on patent WO 9948519

Abstract (Basic): WO 9948519 A1

NOVELTY - Method for producing a sustained release composition (A) comprising dispersing a physiologically active polypeptide (I) in an organic solution of a biodegradable polymer (II), and then removing the solvent, is new.

DETAILED DESCRIPTION - Method for producing a sustained release composition (A) comprising dispersing a physiologically active polypeptide (I) in an organic solution of a biodegradable polymer (II), and then removing the solvent. (I) is a powder produced by lyophilizing an aqueous solution of (I) that contains a water-soluble solvent and/or a volatile salt.

INDEPENDENT CLAIMS are also included for the following:

(a) the sustained release composition (A), produced by the above method;

(b) a method for producing powdered (I) by lyophilizing a solution containing water-soluble organic solvent and/or volatile salt;

(c) the powdered (I) produced by the method of (b); and

(d) sustained release compositions (A') containing (I) and a polyvalent metal salt of (II) in which the initial release rate is not over 40%.

USE - (A) is useful for the delivery of a growth hormone (GH) to a subject, e.g. for the treatment of Turner's syndrome, chronic renal disease, achondroplasia, hypopituitarism, pituitary dwarfism, Down's and Silver syndromes, hypochondroplasia, juvenile chronic arthritis and congestive heart failure. Many other polypeptides may also be delivered, e.g. for treatment of diabetes , viral hepatitis, cancer, anemia, fractures, ulcers, infections etc. (A) are useful in human or veterinary medicine .

ADVANTAGE - (A) release (I) over a period of 1 week to 1 month, provide a high and stable concentration of (I) with low initial release rate and effectively entrap (I). Powdered (I) has a very small particle size, is easy to handle and is suitable for large scale production of (A). The addition of the water-soluble solvent or volatile salt during lyophilization ensures the retention of physiological activity.

pp; 53 DwgNo 0/2

Derwent Class: A96; B04; B07; C03; C07
International Patent Class (Main): A61K-000/00; A61K-038/27
International Patent Class (Additional): A61K-009/16; A61K-009/19; A61K-009/52; A61K-038/00; A61K-047/18; A61K-047/30; C07K-014/61

3/7/28 (Item 14 from file: 351)
DIALOG(R)File 351:Derwent WPI

012496517
WPI Acc No: 1999-302625/199925
Encapsulating active substance in biodegradable polymer to give sustained release particles
Patent Assignee: BIOGLAN THERAPEUTICS AB (BIOG-N); BIOGLAN AB (BIOG-N); BIOGRAM AB (BIOG-N)
Inventor: LAAKSO T; RESLOW M
Number of Countries: 085 Number of Patents: 013
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9920253	A1	19990429	WO 98SE1717	A	19980924	199925	B
SE 9703874	A	19990424	SE 973874	A	19971023	199929	
ZA 9809199	A	19990630	ZA 989199	A	19981008	199931	
AU 9894670	A	19990510	AU 9894670	A	19980924	199938	
SE 512663	C2	20000417	SE 973874	A	19971023	200026	
NO 200002039	A	20000613	WO 98SE1717	A	19980924	200041	
			NO 20002039	A	20000418		
EP 1033973	A1	20000913	EP 98948005	A	19980924	200046	
			WO 98SE1717	A	19980924		
CZ 200001352	A3	20001011	WO 98SE1717	A	19980924	200060	
			CZ 20001352	A	19980924		
AU 732891	B	20010503	AU 9894670	A	19980924	200129	
NO 310177	B1	20010605	WO 98SE1717	A	19980924	200134	
			NO 20002039	A	20000418		
HU 200004732	A2	20010528	WO 98SE1717	A	19980924	200140	
			HU 20004732	A	19980924		
KR 2001031289	A	20010416	KR 2000704276	A	20000420	200163	
JP 2001520186	W	20011030	WO 98SE1717	A	19980924	200202	
			JP 2000516653	A	19980924		

Priority Applications (No Type Date): SE 973874 A 19971023
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9920253	A1	E	31	A61K-009/14	

Designated States (National): AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK

LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

ZA 9809199	A	29	A61K-000/00	
AU 9894670	A			Based on patent WO 9920253
SE 512663	C2		A61K-009/14	
NO 200002039	A		A61K-000/00	
EP 1033973	A1 E		A61K-009/14	Based on patent WO 9920253
Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE				
CZ 200001352	A3		A61K-009/14	Based on patent WO 9920253
AU 732891	B		A61K-009/14	Previous Publ. patent AU 9894670 Based on patent WO 9920253
NO 310177	B1		A61K-009/14	Previous Publ. patent NO 200002039
HU 200004732	A2		A61K-009/14	Based on patent WO 9920253
KR 2001031289	A		A61K-009/14	
JP 2001520186	W	29	A61K-009/51	Based on patent WO 9920253

Abstract (Basic): WO 9920253 A1

NOVELTY - Encapsulating an active substance in a biodegradable polymer comprises:

(a) dissolving the polymer in an organic solvent;

(b) (i) dispersing the active substance in, or (ii) emulsifying the active substance in water or an aqueous solvent with, the solution from (a) to give a dispersion or an emulsion respectively with the active substance as the inner phase;

(c) encapsulating the product from (b) using an aqueous polyethylene glycol solution as a continuous phase to give micro- or nanoparticles.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for sustained release micro- or nano-particles prepared by the above process.

USE - For encapsulating soluble and highly insoluble active substances e.g. drugs , peptides, pesticides, fragrances, flavoring agents, catalysts or herbicides to allow sustained release.

ADVANTAGE - The process allows high incorporation efficiency and/or gives smaller microparticles and even nanoparticles containing highly active doses of agent. The amount of organic solvent and energy required is reduced compared to prior art processes. The process also avoids the use of PVA or other surfactants.

pp; 31 DwgNo 0/1

Derwent Class: A25; A28; A32; A96; A97; B04; B07; C07; D13; D16; D23
International Patent Class (Main): A61K-000/00; A61K-009/14; A61K-009/51
International Patent Class (Additional): A61K-009/50; A61K-031/7064; A61K-031/7088; A61K-031/711; A61K-038/00; A61K-038/04; A61K-038/21; A61K-038/22; A61K-038/27; A61K-038/28; A61K-038/43; A61K-039/00; A61K-047/34; B01J-013/00; B01J-013/02

3/7/29 (Item 15 from file: 351)
DIALOG(R)File 351:Derwent WPI

012125465 **Image available**
WPI Acc No: 1998-542377/199846
Sustained release delivery system for delivering beneficial agent e.g. protein - has capillary channel communicating with reservoir and exterior of system
Patent Assignee: ALZA CORP (ALZA)
Inventor: BROWN J E; DAVIS C R; DIONNE K E; PRSTRELSKI S J; ROORDA W E;

TZANNIS S T; WRIGHT J C; PRESTRELSKI S J
Number of Countries: 082 Number of Patents: 010
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9843611	A1	19981008	WO 98US5138	A	19980317	199846	B
AU 9865588	A	19981022	AU 9865588	A	19980317	199910	
US 5972369	A	19991026	US 9742196	A	19970331	199952	
			US 9850101	A	19980330		
EP 973499	A1	20000126	EP 98911690	A	19980317	200010	
			WO 98US5138	A	19980317		
CN 1251986	A	20000503	CN 98803906	A	19980317	200036	
AU 729870	B	20010215	AU 9865588	A	19980317	200115	
MX 9908957	A1	20000101	MX 998957	A	19990929	200115	
KR 2001005834	A	20010115	KR 99708908	A	19990929	200151	
NZ 500018	A	20010727	NZ 500018	A	19980317	200151	
			WO 98US5138	A	19980317		
JP 2001518880	W	20011016	JP 98541675	A	19980317	200176	
			WO 98US5138	A	19980317		

Priority Applications (No Type Date): US 9742196 P 19970331; US 9850101 A 19980330
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9843611	A1	E	28	A61K-009/00	
Designated States (National): AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
Designated States (Regional): AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
AU 9865588	A				Based on patent WO 9843611
US 5972369	A			A61F-002/02	Provisional application US 9742196
EP 973499	A1	E			Based on patent WO 9843611
Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE					
CN 1251986	A			A61K-009/00	
AU 729870	B			A61K-009/00	Previous Publ. patent AU 9865588 Based on patent WO 9843611
MX 9908957	A1			A61K-009/00	
KR 2001005834	A			A61K-009/00	
NZ 500018	A			A61K-009/00	Based on patent WO 9843611
JP 2001518880	W		29	A61K-009/00	Based on patent WO 9843611

Abstract (Basic): WO 9843611 A

Sustained release delivery system for delivering a beneficial agent at a predetermined rate comprises: (a) a reservoir comprising the beneficial agent; (b) a capillary channel in communication with the reservoir and the exterior of the system for delivering the beneficial agent from the system; and (c) an outer surface that is impermeable and non-porous during delivery of the beneficial agent. The capillary channel has a cross-sectional area and a length selected to provide the predetermined rate. Also claimed is a sustained release delivery system for delivering a beneficial agent formulated in a glassy sugar matrix at a predetermined rate which comprises: (a) a reservoir comprising the beneficial agent and (b) a capillary channel in communication with the reservoir and the exterior of the system for delivering the beneficial agent from the system. The capillary channel has a cross-sectional area and a length selected to provide the predetermined rate.

The beneficial agent is preferably cidofovir or a protein or peptide. The protein is preferably occluded in a glassy sugar matrix. The capillary channel is filled with the beneficial agent, an

immobilised gel capable of diffusing the beneficial agent or water. The capillary channel is preferably helical. The outer surface is a metal, ceramic, glass or polymer , preferably a bioerodible polymer such as poly(glycolic acid), poly(lactic acid), copolymers of lactic/glycolic acid, polyorthoesters, polyanhydrides, polyphosphazones and polycaprolactones. The non-porous material is titanium or a titanium alloy. The system may be implanted into a mammalian organism.

USE - The system is used in producing a controlled and sustained release of beneficial agents in obtaining a desired local or systemic physiological or pharmacological effect relating at least to treatment of cancerous primary tumours, chronic pain, arthritis, rheumatic conditions, hormonal deficiencies such as diabetes and dwarfism and modification of the immune response such as in the prevention of transplant rejection and in cancer therapy . The beneficial agent delivery system is particularly used for direct implantation into the vitreous humour of the eye and for application to an intraocular lens. Administration is e.g. intraocular, oral, subcutaneous, intramuscular, intraperitoneal or dermal. The system is capable of continuously delivering 0.5-2 mu g/day of the beneficial agent. The system is capable of continuous delivery for a period of at least 2 years.

ADVANTAGE - The system can be used to deliver hydrophilic molecules, which are notoriously different to deliver from a membrane controlled diffusional system. There are no moving parts in the system and so it is easier to fabricate than plunger-type osmotic delivery systems. As long as the protein is inside the delivery system, it is protected either by the glassy sugar matrix or by the presence of the dissolved stabiliser molecules that once formed the sugar matrix.

Dwg.1/4

Derwent Class: A96; B04; B07; P32; P34
International Patent Class (Main): A61F-002/02; A61K-009/00
International Patent Class (Additional): A61F-009/007; A61K-009/22; A61K-031/675; A61K-038/00; A61K-047/02; A61K-047/04; A61K-047/34; A61M-037/00; A61P-031/18

3/7/30 (Item 16 from file: 351)
DIALOG(R)File 351:Derwent WPI

011511483
WPI Acc No: 1997-489398/199745
Protein adsorbed onto lactate copolymer grains used as scleral plug for intra-ocular surgery - during treatment of retinal disease, release of medicaments and extraction of vitreous matter
Patent Assignee: SANTEN PHARM CO LTD (SANT)
Inventor: KUNOU N; OGURA Y; OTA A
Number of Countries: 024 Number of Patents: 004
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9735621	A1	19971002	WO 97JP939	A	19970319	199745	B
JP 9255555	A	19970930	JP 9668609	A	19960325	199749	
EP 904787	A1	19990331	EP 97908497	A	19970319	199917	
			WO 97JP939	A	19970319		
JP 2001151693	A	20010605	JP 9668609	A	19960325	200138	
			JP 2000370834	A	19960325		

Priority Applications (No Type Date): JP 9668609 A 19960325; JP 2000370834 A 19960325
Cited Patents: JP 558882; JP 6312943
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9735621	A1	J	17	A61K-047/30	
Designated States (National): CA CN KR NO US					
Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
JP 9255555	A		5	A61K-009/00	
EP 904787	A1	E		A61K-047/30	Based on patent WO 9735621
Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 2001151693	A		5	A61K-038/21	Div ex application JP 9668609

Abstract (Basic): WO 9735621 A

A composition (I) comprises a protein material adsorbed onto the surface of microfine grains of lactic acid copolymer . Also claimed is a scleral plug prepared using (I).

USE - The scleral plug is used in the prevention and treatment of intraocular diseases, as a means for releasing medicaments (e.g. interferon- beta and IFN- beta), in the extraction of the vitreous body or in the treatment of retinal disease (e.g. diseases associated with diabetes , macular degeneration, or vascular occlusion) (all claimed).

ADVANTAGE - The protein is protected from loss of activity due to heat or organic solvent.

Dwg.0/0

Derwent Class: A96; B04; B07; D22
International Patent Class (Main): A61K-009/00; A61K-038/21; A61K-047/30
International Patent Class (Additional): A61K-038/00; A61K-047/34; A61P-027/02

3/7/31 (Item 17 from file: 351)
DIALOG(R)File 351:Derwent WPI

008645935
WPI Acc No: 1991-149964/199121
Injectable, biodegradable microspheres - contg. copolymer of lactic- and glycolic-acids and anti-oestrogen or anti-progestomimetic steroid
Patent Assignee: ROUSSEL-UCLAF (ROUS)
Inventor: COHEN G; DUBOIS J; DUBOIS J L
Number of Countries: 013 Number of Patents: 015
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
DE 4036425	A	19910516	DE 4036425	A	19901115	199121	B
NL 9002492	A	19910603	NL 902492	A	19901115	199125	
LU 87836	A	19910507				199127	
GB 2239798	A	19910717	GB 9024868	A	19901115	199129	
CA 2029940	A	19910516				199130	
DK 9002709	A	19910516				199132	
FR 2654337	A	19910517	FR 8914976	A	19891115	199132	
SE 9003570	A	19910516				199142	
JP 3294229	A	19911225	JP 90306374	A	19901114	199207	
CH 681691	A5	19930514	CH 903611	A	19901114	199326	
BE 1005511	A4	19930831	BE 901062	A	19901109	199340	
GB 2239798	B	19931027	GB 9024862	A	19901115	199343	
IT 1242010	B	19940202	IT 9048470	A	19901113	199436	
AT 9002313	A	19950415	AT 902313	A	19901115	199520	
AT 400298	B	19951015	AT 902313	A	19901115	199546	

Priority Applications (No Type Date): FR 8914976 A 19891115
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
BE 1005511	A4		27	A61K-000/00	
AT 400298	B			A61K-009/58	Previous Publ. patent AT 9002313
CH 681691	A5			A61K-009/52	
GB 2239798	B			A61K-031/565	
IT 1242010	B			A61K-000/00	
AT 9002313	A			A61K-009/58	

Abstract (Basic): DE 4036425 A

Injectable, biologically degradable microspheres which can be used to prepare a medicament with antioestrogen or antiprogestomimetic activity comprise (a) a copolymer of lactic-and glycolic- acids; and (b) an antioestrogen or antiprogestomimetic steroid.

USE/ADVANTAGE - Microspheres can be used in injectable solns. for the long-term treatment of diseases which require a progressive and constant release of active ingredient. The microspheres contg. the antiprogestomimetic steroid can be used for the treatment of hormonal disturbances endometrioses and hormone-dependent microsphers contg. the antioestrogen steroid can be used in the treatment of disorders associated with hypersecretion of glucocorticoids esp. against ageing esp. against hypertension, atherosclerosis, osteoporosis, diabetes , obesity, redn. in immunity and insomnia. The microspheres can be injected subcutaneously or intramuscularly.

Dwg.0/1

Abstract (Equivalent): GB 2239798 B

Microspheres for providing a medicament having an anti-progestomimetic activity, which microspheres comprise: - a lactic acid and glycolic acid copolymer , and - an anti-progestomimetic steroid, substituted in position 11beta and optionally in position 2, corresponding to the general formula (I) in which R1 represents an organic radical containing from 1 to 18 carbon atoms and optionally one or more heteroatoms, the atom immediately adjacent to the carbon in position 11 being a carbon atom, R2 represents a hydrocarbon radical containing from 1 to 8 carbon atoms, X represents the remainder of a pentagonal or hexagonal ring optionally substituted and optionally carrying an unsaturation, the rings A and B having one of the following structures: a) - either A and B represent the group (1) in which R' and R'', which may be the same or different, represent an hydrogen atom, or an alkyl radical having from 1 to 4 carbon atoms; b) - or A and B represent the group: (ii) Rx representing a hydrogen atom or a group -ORe, in which Re represents a hydrogen atom, an optionally substituted alkyl radical having from 1 to 6 carbon atoms or an acyl radical; c) - or A and B represent the group: (iii) as well as the addition salts of the compounds of formula (IA) with acids.

Dwg.0/0

Derwent Class: A96; B01; B07
International Patent Class (Main): A61K-009/52; A61K-031/565
International Patent Class (Additional): A61K-009/10; A61K-009/58; A61K-031/56; A61K-047/12

3/7/32 (Item 18 from file: 351)
DIALOG(R)File 351:Derwent WPI

008642118
WPI Acc No: 1991-146148/199120
Enteric prepn. to release drug (s) in large intestine - based on biologically modified absorptive polymeric aliphatic polyester as enteric coating of base
Patent Assignee: BIOMATERIAL UNIVERS (BIOM-N)

Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
JP 3083917	A	19910409	JP 89222643	A	19890829	199120	B

Priority Applications (No Type Date): JP 89222643 A 19890829

Abstract (Basic): JP 3083917 A

The aliphatic polyesters which are decomposed and absorbed in the living body are polylactic acid, polyglycolic acid, lactic acid /glycolic acid copolymers , polymalic acid, poly-epsilon-caprolactone, lactic acid /caprolactone copolymers , glycolic acid/caprolactone copolymers , poly-beta-hydroxybutyrate, hydroxybutyrate/valerate copolymers , polydepsipeptides, poly-alpha-cyanoacrylate, polyacid anhydrides, are polyethylene glycol/ lactic acid copolymers . Method for enteric prepns. has solid agents coated by using the enteric coating bases.

The solid agents are polypeptide or proteinous drugs , antibacterials, antitumour drugs , antipyretic antiinflammatory analgesic drugs , antitussive expectorants, antidepressants, muscle relaxants, antiulcerics, antiallergics, hypotensive diuretics, antidiabetics , cardiotonics, vasodilators, antiarrhythmics, blood anticoagulants, hemostatics, narcotic antagonists, anti-tuberculosis drugs , hormone drugs , immunostimulants, antiepileptics, antihistamics, and contrast media.

Method for enteric prepns. which are obtainable by extrusion, calendering, or casting mould process using the enteric coating base films and the aliphatic polyesters alone or in admixture with plasticisers or with powders. The plasticisers are triacetin, sugar esters, phthalic acid esters, polyethylene glycol, propylene glycol, citric acid triethyl, tartaric acid diethyl, or their mixtures.

USE/ADVANTAGE - The enteric prepns. are new types whichevade the decomposition and absorption of drugs in the stomach and small intestines, and the drugs are released when reaching the large intestines. This selective absorption occurs due to the coating of the drugs with polylactic acid-type polymers. Efficacy is thus manifested of active peptides which cannot be used by oral administration.

Dwg.0/0

Derwent Class: A96; B07
International Patent Class (Additional): A61K-009/32; A61K-047/34

3/7/33 (Item 19 from file: 351)
DIALOG(R)File 351:Derwent WPI

007985179
WPI Acc No: 1989-250291/198935
Controlled-release microspheres - contg. polylactic acid and water-soluble active agent
Patent Assignee: BIOMATERIALS UNIVERSE INC (BIOM-N)
Inventor: HYON S; IKADA Y; HYON S H
Number of Countries: 009 Number of Patents: 007
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
EP 330180	A	19890830	EP 89103091	A	19890222	198935	B
JP 1216918	A	19890830	JP 8842459	A	19880224	198941	
US 5100669	A	19920331	US 89315167	A	19890224	199216	
EP 330180	B1	19930113	EP 89103091	A	19890222	199302	
DE 68904326	E	19930225	DE 604326	A	19890222	199309	
			EP 89103091	A	19890222		

JP 2670680	B2	19971029	JP 8842459	A	19880224	199748
EP 330180	B2	19990303	EP 89103091	A	19890222	199913

Priority Applications (No Type Date): JP 8842459 A 19880224
Cited Patents: EP 134318; EP 145240; EP 274961; EP 58481; JP 57150609; JP 60100516
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
EP 330180	A	E	12		
Designated States (Regional): CH DE FR GB IT LI NL					
US 5100669	A		7		
EP 330180	B1	E	12	A61K-009/16	
Designated States (Regional): CH DE FR GB IT LI NL					
DE 68904326	E			A61K-009/16	Based on patent EP 330180
JP 2670680	B2		7	A61K-009/52	Previous Publ. patent JP 1216918
EP 330180	B2	E		A61K-009/16	
Designated States (Regional): CH DE FR GB IT LI NL					

Abstract (Basic): EP 330180 A

Microspheres with a mean particle size of 0.01-300 microns comprise polylactic acid (I) and a water-soluble physiologically active substance (II).

Pref. (I) is selected from homopolymers of L- or DL- lactic acid and their copolymers with glycolic acid. The microspheres are produced by (a) dissolving (I) and (II) in an organic acid (esp. acetic or formic acid) or in a mixt. of H2O and a hydrophilic organic solvent; (b) mixing the soln. with an immiscible nonsolvent to form an o/o or w/o emulsion; and (c) evaporating the emulsion.

USE - The microspheres are useful for controlled release of drugs or agricultural chemicals.

0/0

Abstract (Equivalent): EP 330180 B

A microsphere which comprises polylactic acid selected from the group consisting of an L- lactic acid polymer , a D,L- lactic acid polymer , a copolymer of L- lactic acid and glycolic acid and a copolymer of D,L- lactic acid and glycolic acid, and a water soluble physiologically active substance, selected from the group consisting of a polypeptide type or proteinaceous substance, an antimicrobial agent, an antitumor agent, an antipyretic, an antiinflammatory agent, an analgesic, an antitussive, an expectorant, an antidepressant, a muscle relaxant, an antiulcer agent, an antiallergic agent, a hypotensive, a diuretic, an antidiabetic , a cardiotonic, a vasodilating agent, an antiarrhythmic agent, an anticoagulating agent, a hemostatic agent, a narcotic antagonist, an antitubercular agent, a hormone, an immunoactivator, an antiepileptic agent, an antihistaminic and an agricultural agent, and has a mean particles size of from about 0.01 micro-m to 300 micro-m having not more than 30% of an eluted amount of said physiologically active substance based on the content of said physiologically active substance in the microsphere after 24 hours in in vitro elution test in phosphate buffer of pH 7.4 at 37 deg.C. (Dwg.0/0)

Abstract (Equivalent): US 5100669 A

Prodn. of microspherules of polylactic acid and a water-soluble physiologically active substance, e.g. drug , comprises dissolving polylactic acid and the water-soluble drug in aq. MeCN or aq. HOAc; dispersion of the soln. with a water-immiscible solvent (e.g. silicone oil, paraffin, cotton oil, sesame oil, castor oil, cone oil, whale oil, toluene, xylene or hexane) to form an oil in oil or aq./oil emulsion; and evapn. of the volatile components.

USE - Prods. are drug compsns. for slow drug release over long periods (1 week or more) in vivo. ()A

Derwent Class: A23; A96; A97; B04; B07; C03
International Patent Class (Main): A61K-009/16; A61K-009/52
International Patent Class (Additional): A61K-009/50; A61K-047/00; A61K-047/34; B01J-013/12

3/7/34 (Item 20 from file: 351)
DIALOG(R)File 351:Derwent WPI

004321257
WPI Acc No: 1985-148135/198525
Prolonged release microcapsules contg. water soluble drug - are obtd. from water-in-oil emulsion contg. gelatin, polymer etc
Patent Assignee: TAKEDA CHEM IND LTD (TAKE)
Inventor: OGAWA Y; OKADA H; YUASHIKI T; YASHIKI T
Number of Countries: 017 Number of Patents: 016
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
EP 145240	A	19850619	EP 84307570	A	19841102	198525	B
JP 60100516	A	19850604	JP 83207760	A	19831104	198528	
PT 79450	A	19851122				198551	
HU 37037	T	19851128				198604	
ES 8605983	A	19861001	ES 537325	A	19841102	198649	
US 4652441	A	19870324	US 84667096	A	19841101	198714	
US 4711782	A	19871208	US 86940614	A	19861211	198751	
CA 1233414	A	19880301				198813	
EP 145240	B	19890419				198916	
DE 3477732	G	19890524				198922	
JP 89057087	B	19891204				199001	
US 4917893	A	19900417	US 87103117	A	19870930	199020	
US 5061492	A	19911029	US 90469784	A	19900124	199146	
US 5476663	A	19951219	US 84667096	A	19841101	199605	
			US 86940614	A	19861211		
			US 87103117	A	19870930		
			US 90469784	A	19900124		
			US 91748423	A	19910822		
			US 94228452	A	19940415		
US 5631021	A	19970520	US 84667096	A	19841101	199726	
			US 86940614	A	19861211		
			US 87103117	A	19870930		
			US 90469784	A	19900124		
			US 91748423	A	19910822		
			US 94228452	A	19940415		
			US 95468657	A	19950606		
			US 96604022	A	19960220		
US 5631020	A	19970520	US 84667096	A	19841101	199726	
			US 86940614	A	19861211		
			US 87103117	A	19870930		
			US 90469784	A	19900124		
			US 91748423	A	19910822		
			US 94228452	A	19940415		
			US 95468657	A	19950606		

Priority Applications (No Type Date): JP 83207760 A 19831104
Cited Patents: A3...8527; EP 52510; FR 2491351; GB 929402; No.SR.Pub; US 3523906
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
EP 145240	A	E	35		

Designated States (Regional): AT BE CH DE FR GB IT LI LU NL SE

EP 145240	B E		
Designated States (Regional): AT BE CH DE FR GB IT LI LU NL SE			
US 5476663	A	10 A61K-009/52	Div ex application US 84667096
			Div ex application US 86940614
			Div ex application US 87103117
			Div ex application US 90469784
			Cont of application US 91748423
			Div ex patent US 4652441
			Div ex patent US 4711782
			Div ex patent US 4917893
			Div ex patent US 5061492
US 5631021	A	10 A61K-009/14	Div ex application US 84667096
			Div ex application US 86940614
			Div ex application US 87103117
			Div ex application US 90469784
			Cont of application US 91748423
			Div ex application US 94228452
			Div ex application US 95468657
			Div ex patent US 4652441
			Div ex patent US 4711782
			Div ex patent US 4917893
			Div ex patent US 5061492
			Div ex patent US 5476663
US 5631020	A	9 A61K-009/14	Div ex application US 84667096
			Div ex application US 86940614
			Div ex application US 87103117
			Div ex application US 90469784
			Cont of application US 91748423
			Div ex application US 94228452
			Div ex patent US 4652441
			Div ex patent US 4711782
			Div ex patent US 4917893
			Div ex patent US 5061492
			Div ex patent US 5476663

Abstract (Basic): EP 145240 A

Prolonged release microcapsule is obtd. by prepn. of a water-in-oil emulsion comprising an inner aq. layer contg. a water-soluble drug (I) and a drug retaining substance (II) and an oil layer contg. a high-polymer substance (III). The inner aq. layer is thickened or solidified to a viscosity of not lower than 5000 centipoises. Then the emulsion is subjected to water drying.

USE/ADVANTAGE - The prolonged release microcapsule is obtd. with good efficiency when the thickening or solidifying step is used (see E.P.52510). (I) may be any water-soluble drug , and it is esp. a polypeptide of molecular wt. 200-80000, e.g. luteinising hormone releasing hormone and its derivs.

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Abstract (Equivalent): EP 145240 B

A prolonged release microcapsule, which is produced by prepg a water-in-oil emulsion comprising an inner aq layer contg a water-soluble drug and a drug retaining substance therefor and an oil layer contg a high polymer substance, then thickening or solidifying said inner aq layer to a viscosity of not lower than 5.0 Pas (5000 centipoises) and finally subjecting the resulting emulsion to in water drying. (15pp)i

Abstract (Equivalent): US 5631021 A

A prolonged release microcapsule for injection, which is produced by redispersing a spherical microcapsule having an average diameter of 2 to 200 mu m, comprising particles containing a water-soluble drug , the particles being dispersed in a spherical microcapsule matrix

composed of a polymer of lactic acid and glycolic acid having a comonomer ratio within the range of about 100/0 to 50/50 and an average molecular weight within the range of about 5,000 to 200,000, in an excipient selected from the group consisting of mannitol, sorbitol, lactose and glucose and then solidifying, wherein, the water-soluble drug is a polypeptide of the formula (I)

(Pyr)Glu-R1-Trp-Ser-R2-R3-R4-Arg-Pro-R5(I)

wherein R1 is His, Tyr, Trp or p-NH2-Phe; R2 is Tyr or Phe; R3 is Gly or a D-amino acid residue; R4 is Leu, Ile or Nle; and R5 is Gly-NH-R6 or NH-R6, wherein R6 is H or a lower alkyl group which may optionally be substituted by OH, or a salt thereof, and the resulting microcapsule, upon reconstitution in a vehicle for injection, provides greater stability than if no redispersing step is performed.

Dwg.0/0

US 5631020 A

A method for producing a prolonged release microcapsule for injection, which comprises redispersing a spherical microcapsule having an average diameter of 2 to 200 mu m, comprising particles containing a water-soluble drug , the particles being dispersed in a spherical microcapsule matrix composed of a polymer of lactic acid and glycolic acid having comonomer ratio within the range of about 100/0 to 50/50 and an average molecular weight within the range of about 5,000 to 200,000, in an excipient selected from the group consisting of mannitol, sorbitol, lactose and glucose and then solidifying,

wherein he resulting microcapsule upon reconstitution in a vehicle for injection, provides greater stability than if no redispersing step is performed, and

wherein the water-soluble drug is (Pyr) Glu-His-Trp-ser-Tyr-D-Leu-Leu-Arg-Pro-NH-C2H5Dwg.0/0

US 5476663 A

A prolonged release microcapsule for injection, which comprises particles containing a water-soluble drug , the particles being dispersed in a spherical microcapsule matrix composed of a copolymer of lactic acid and glycolic acid having a comonomer ratio within the range of about 100/0 to 50/50 and an average molecular weight within the range of about 5,000 to 200,000, the spherical microcapsule matrix having an average diameter of 2 to 200 mum, and an excipient selected from the group consisting of mannitol, sorbitol, lactose and glucose, which particles are produced by in-water drying.

Dwg.0/0

US 5061492 A

Injectable compsns. comprise spherical microcapsules and a pharmaceutically acceptable vehicle. The microcapsules are of ave. dia. 2-200 microns. They comprise particles of a mixt. of (a) a water-soluble, non-polypeptide drug and (b) a drug -retaining substance.

(b) is gelatin, albumin, pectin or agar. The wt. ratio (b):(a) is 9:1-0.3:1. The particles are dispersed in a matrix of a biodegradable polymer (I). (I) is a copolymer of lactic acid and glycolic acid having a comonomer ratio of 100:0 to 50:50 and an ave. mol. wt. of 5,000-200,000.

USE - For administering antibiotics, antitumour agents, antipyretics, analgesics, anti-inflammation, antitussives, expectorants, sedatives, muscle relaxants, antiepileptics, antiulcer agents, antidepressants, antiallergic drugs , cardiotonics, antiarrhythmics, vasodilators, antihypertensives, diuretics, antidiabetics , anticoagulants, haemostatics, antituberoltics, hormone drugs and antinarcotis. Pref. drugs are mitomycin C, sulpyrine, morphine hydrochloride and sodium diclofenacUS 4917893 A

Pharmaceutical compsn. comprises one or more active substances, e.g. luteinising hormone releasing hormone or its derivs., (1 pt.wt)

and a supporting medium (1-2.5 pts. wt.), e.g. gelatine, albumin, pectin or agar, dispersed in a spherical microcapsule copolymer matrix (mean diam. 2-200 micro-m) obtd. from lactic acid (78-50 wt.%) and glycollic acid (22-50 wt.%) and having Mr 5,000-100,000.

USE - The prods. are slow release compsns. having a long lifetime in the body. (11pp)r

US 4711782 A

Prolonged release microcapsule of dia. 0.5-400 microns for injection, is produced from a water-in-oil emulsion contg. (a) an inner aq. layer contg. a water-soluble and non-poly-peptidic drug ; (b) gelatin, albumin, pectin or agar as a drug -retaining substance: and (c) on oil layer contg. a lactic acid -glycolic acid copolymer or lactic acid polymer .

Process comprises (i) thickening or solidifying (a) to viscosity 5000 cP or more; (ii) admixing emulsion obtd. with a third aq. layer to form a water/oil/water ternary layer emulsion; then (iii) desorbing solvent in oil layer.

USE - To esp. release mitomycin C, sulpyrine, morphine hydrochloride, or sodium diclofenae. (11ppUS 4652441 A

Pharmaceutical compsn. comprises one or more active polypeptides (etc.) with the usual inert carriers and opt. additives, encapsulated to form microspherules (dia. 0.002-0.200 mm). Prepn. of these compsns. comprises dispersing the biologically active polypeptide with aq. gelatin, albumin, pectin or agar, and an immiscible volatile solvent contg. lactic acid -glycollic acid copolymer or polylactic acid; the inner aq. phase is thickened (viscosity at least 5000 cP) or solidified by physical means or additives; the resulting water-in-oil emulsion is then dispersed with an aq. medium to form a ternary system, and the solvent in the oil phase is evapd. at reduced pressure in a rotatory evaporator.

USE - The prods. are suitable for injection, and provide a gradual release of active substances into the body. (11pp)e

Derwent Class: A96; B07; P32
International Patent Class (Main): A61K-009/14; A61K-009/52
International Patent Class (Additional): A61F-002/00; A61K-009/50; A61K-037/38; A61K-047/00; B01J-013/02; C07K-007/20

3/7/35 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0226731 DBA Accession No.: 98-08328 PATENT
Isolation of insulin by high-pressure liquid chromatography - recombinant insulin purification, for use in therapy
AUTHOR: Obermeier R; Ludwig J; Sabel W
CORPORATE SOURCE: Frankfurt, Germany.
PATENT ASSIGNEE: Hoechst 1998
PATENT NUMBER: EP 849277 PATENT DATE: 980624 WPI ACCESSION NO.: 98-324604 (9829)
PRIORITY APPLIC. NO.: DE 10652713 APPLIC. DATE: 961218
NATIONAL APPLIC. NO.: EP 97121847 APPLIC. DATE: 971211
LANGUAGE: German
ABSTRACT: A new method for isolation of human or recombinant insulin (formula specified) by chromatography involves using a pressure-stable acidic cation-exchanger at a pressure of 1.1-40 MPa. The insulin is isolated in a form pure enough for direct preparation of injectable solutions. The cation-exchanger is a crosslinked styrene-divinylbenzene copolymer with sulfonic acid groups, and is loaded with 5-15 g protein/l column volume at a pH of 2.5-5.5, preferably 3.5-4. The column is eluted with a water and alcohol mixture containing 10-50,

especially 25-35 vol% of a 1-4C alcohol, preferably ethanol or isopropanol, especially propanol. The eluent has a pH of 3.5-4. The loading solution and eluent contain a buffer, preferably based on an organic acid, especially lactic acid . The column is eluted with an ammonium or alkali metal salt gradient of 0-0.8 M, especially 0.1-0.25 M. (12pp)

3/7/36 (Item 1 from file: 453)
DIALOG(R)File 453:Drugs of the Future

00090141 (Structure Image Available)
ENTRY NUMBER: 90141
DRUG NAME: AM-833
Ro-236240
Ro-23-6240/000
GENERIC NAME Fleroxacin (recommended INN; BAN; USAN)
BRAND NAME: Megalocin (Kyorin, JP)
Megalone (Roche, US)
Megalosin (Kyorin, JP)
Quinodis (Roche, CH)
CHEM NAME: 6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
FORMULA: C17H18F3N3O3
CAS REG. NO.: 79660-72-3
79660-53-0 (monoHCl)
DEVEL. PHASE: Launched (201992)
ORIGINATOR: Kyorin
LICENSEE: Roche
CLASS: 68000 (Antibacterial Drugs)
68210 (Quinolones)
SYNTHESIS: 11018
CONTEXT TABLE: 68210C (Fluoroquinolones)

Against Gram-positive and Gram-negative clinical isolates, activity of fleroxacin was found to be similar to that of ofloxacin; compound exhibited excellent activity against H. influenzae and no activity against beta-hemolytic streptococci. Resistance in E. coli and S. marcescens was also evaluated. (2)

In 5 healthy male volunteers administered fleroxacin 800 mg/day b.i.d. for 7 days, total number of anaerobic and aerobic bacteria in feces was found to decrease during treatment, but return to pretreatment levels after withdrawal. No outgrowth of C. difficile was observed. Sensitivity of aerobic and anaerobic isolates to compound was similar before and after administration. (4)

Fifty-seven men and women with non-gonococcal urethritis, mucopurulent cervicitis or infection with C. trachomatis (or sexual contacts with such individuals) were entered in a double-blind trial of fleroxacin 400, 600 or 800 mg once daily for 7 days. In initially infected patients cultures were negative at followup in 9 of 15 men and 5 of 5 women with C. trachomatis, in 10 of 12 men and 8 of 11 women with Ureaplasma, and in 3 of 3 men and 3 of 5 women with M. hominis. Adverse effects, most frequent being insomnia,nausea and lightheadedness, were reported in 33 of 39 men and 14 of 17 women, and 2 cases of severe photosensitivity reactions were reported. (5)

In 6 healthy male volunteers administered fleroxacin 400 mg orally, compound was found to be rapidly absorbed, with mean peak serum

levels of 6.1 mcg/ml reached at 0.7 h and elimination half-life of 12.0 h. Compound penetrated rapidly into inflammatory fluid (89.7%), with peak levels of 3.8 mcg/ml at 4 h. Urinary recovery of fleroxacin, N-desmethylfleroxacin and N-oxide was 49.5, 6.9 and 5.7%, respectively. Twenty patients were administered 400 mg/day for 4 days and mean serum levels of 8.4 mcg/ml were obtained,with mean bronchial mucosa levels of 12.8 mcg/ml. (6)

Rabbits with and without experimental E. coli meningitis were administered 7-h constant infusion of fleroxacin 0.5 or 5 mg/kg/h after a bolus of 15% of total dose. Serum levels of title compound after 0.5 and 5 mg/kg/h were 0.76 +/- 0.35 and 2.1 +/- 1.1 mcg/ml, respectively; serum levels of active N-demethyl metabolite were lower than in CSF and serum levels of N-oxide metabolite exceeded levels of parent compound in some animals. Fleroxacin and N-demethyl metabolite showed good penetration into brain and CSF, while N-oxide metabolite did not. Fleroxacin was effective in treating meningitis, although levels 40 and 6 times greater than MBC did not give different rates of kill in CSF. (7)

In a study of the pharmacokinetics of fleroxacin and its N-demethyl and N-oxide metabolites in 12 elderly patients treated with single oral doses of 800 mg title compound, plasma kinetics were found to be mainly correlated with weight and urinary kinetics with creatinine clearance. Compared to in young patients, t1/2 of all three compounds was unchanged, while volume of distribution and total clearance of fleroxacin and renal clearance of all three compounds were lower in elderly patients, resulting in higher plasma concentrations of compounds in the latter. (8)

Twelve patients with cystic fibrosis and 12 healthy volunteers received single oral doses of 800 mg fleroxacin and 800 mg/day for 5 days. Elimination half-life was significantly lower in patients, as were volume of distribution and total apparent and non-renal clearance. After single doses, peak plasma levels normalized for weight were significantly higher in patients than in healthy subjects, indicating slower and more complete absorption in these patients. (9)

In a trial in 6 healthy subjects and 18 patients with varying degrees of renal impairment administered single oral doses of 400 mg fleroxacin, half-lives of parent compound and N-demethyl and N-oxide metabolites were found to increase with decreasing creatinine clearance, while peak plasma concentrations, time to peak and apparent volume of distribution were minimally affected. AUC was significantly increased for all three compounds (3-50-fold), due to decrease in renal clearance, correlated with creatinine clearance. In 6 patients on hemodialysis, extraction ratios of fleroxacin, N-oxide and N-demethyl metabolites by dialyzer were 27 +/- 3, 43 +/- 8 and 37 +/- 4%, respectively, and clearance was 57 +/- 7, 92 +/- 16 and 80 +/- 7 ml/min, respectively. (10)

Two groups of 9 healthy subjects each received fleroxacin 600 mg once daily orally for 7 days or 600 mg by 1-h i.v. infusion for 7 days, and results suggested that compound is completely absorbed after oral administration, with similar steady-state pharmacokinetic profiles after p.o. and i.v. dosing. (11)

In vitro studies have shown fleroxacin to have high activity against a variety of Gram-negative and Gram-positive organisms, most isolates studied being inhibited by low concentrations. Activity against Gram-negative rods, but not Gram-positive cocci, was affected by pH. (12)

A liquid chromatographic assay for determination of fleroxacin and its N-demethyl and N-oxide metabolites in plasma and urine

has been described and applied successfully in human pharmacokinetic studies. (13)

Twelve healthy young volunteers received single and multiple (every 24 h for 5 days) doses of 400 and 800 mg fleroxacin orally. Peak plasma levels of drug were significantly higher after multiple doses of 800 mg (14.3 vs 8.2 mcg/ml after single dose), and elimination half-life was also increased after 800 mg every 24 h for 5 days (from 13.45 +/- 2.94 after single dose to 15.60 +/- 3.16 h). Mean peak blister fluid levels were also significantly higher after multiple dosing with 400 (3.7 +/- 0.8 mcg/ml after single dose vs. 5.7 +/- 0.9 mcg/ml) and 800 mg (7.7 +/- 1.8 mcg/ml after single dose vs. 12.3 +/- 2.1 mcg/ml). Compound was cleared more slowly after multiple administration of 800 mg, probably due to saturation of apparent non-renal clearance. Compound was well tolerated. (14)

A supplementary issue on fleroxacin has been based on papers presented at the International Congress of Chemotherapy in Istanbul in 1987. In summary, fleroxacin has antibacterial activity similar to that of ofloxacin and norfloxacin and is suitable for once-daily dosing. Initial clinical trials suggest its efficacy in a broad range of bacterial infections. (15)

In a trial in 18 female patients undergoing hysterectomy, levels of fleroxacin in Fallopian tube tissue were found to exceed MIC for most pathogens involved in abdominal infections for > 24 h. (16)

Fleroxacin 400 mg as a single dose was evaluated in 24 patients with acute urethral gonococcal infections. All urethral gonococci were eradicated at 3-4 days after administration and at 9-10 days only 1 patient had N. gonorrhea in throat. At day 9-10 almost all patients were free from clinical symptoms. Compound was well tolerated, 1 patient complaining of transient headache. (17)

Results from in vitro studies indicated that fleroxacin may be active against clinically important species of mycobacteria, especially M. tuberculosis and M. fortuitum; no activity was observed against M. chelonei, similar to other quinolones. (18)

In a study in healthy volunteers fleroxacin was found to have insignificant effects on theophylline pharmacokinetics , possibly the least of the available quinolones. (19)

Fleroxacin 0.4 g as single oral dose was administered to 10 healthy volunteers and 18 patients with varying degrees of renal function impairment. Compound was found to accumulate in patients with renal failure, with significant increase in AUC and decrease in renal clearance; in patients with severe renal failure extrarenal clearance was also decreased. Volume of distribution of fleroxacin was also lower than in volunteers. From results in both volunteers and patients with renal failure it appeared that single-dose therapy of urinary tract infections would be feasible in both groups. (20)

Pharmacokinetics of fleroxacin as a single 400-mg oral dose were evaluated in 10 healthy male volunteers. Mean peak plasma levels of 4.0 +/- 1.3 mg/l were reached at 0.9 +/- 0.4 h, AUC over 12 and 24 h was 25.27 and 37.96 mg/l.h, respectively, half-life was 12.5 +/- 2.4 h,renal clearance in 24 h was 81.9 ml/min, and 4-, 8-, 24- and 48-h urinary recovery of unchanged compound was 13.2, 24.9, 45.4 and 54.8% of dose, respectively. (21)

Fleroxacin 400 mg once daily for 4 days was administered to

20 patients undergoing fiberoptic endoscopy. Serum levels of compound were 3.9-12.5 mg/l and bronchial mucosa levels 5.9-19 mg/l, being higher than serum levels in all but 1 patient. Mean penetration into bronchial mucosa was 158%. (22)

In 10 healthy male volunteers administered single oral doses of fleroxacin and pefloxacin 400 mg in a cross-over, randomized trial time to peak plasma levels and elimination half-life were found to be similar for both compounds, while peak plasma levels and AUC of fleroxacin were significantly greater compared to pefloxacin. Renal clearance of fleroxacin was also significantly greater than that of pefloxacin;48-h urinary recovery of fleroxacin and pefloxacin was 48.6 and 8.6% of dose, respectively, of N-demethyl metabolites 7.1 and 17.4% of dose, respectively, and of N-oxide metabolites 3.8 and 16.6% of dose, respectively. Urinary levels of fleroxacin and its N-demethyl metabolite were 2-3 times higher than those of pefloxacin for 48 h. (23)

MIC90s against C. trachomatis for fleroxacin, T-3262 and NY-198 were found to be 62.5, 0.1 and 3.13 mcg/ml, respectively. (24)

Fleroxacin 400 mg as single oral and multiple doses in young and elderly volunteers exhibited no significant effect on theophylline kinetics. (29)

In a study in 15 elderly volunteers administered fleroxacin 400 mg/day for 7 days results indicated that dose adjustment is not necessary in these subjects. (30)

In vitro activity of fleroxacin against 747 isolates from cancer patients was similar to that of enoxacin and less than that of A-56620 and ciprofloxacin. (31)

An oral single dose of 400 mg of fleroxacin was given to 12 elderly patients. 1-4 h later, plasma concentrations ranged between 0.4 and 5.5 mcg/ml and prostatic adenoma tissue concentrations were slightly higher. (32)

In the rabbit model of methicillin-resistant Staphylococcus aureus endocarditis, fleroxacin at a dose of 30 mg/kg every 8 h or vancomycin at a dose of 17.5 mg/kg every 6 h for 4 days showed to be equally effective in clearing bacteremia, reducing bacterial counts in vegetations and tissues and curing endocarditis. However, resistance to fleroxacin appeared in the test strain of S. aureus in 8% of animals. (33)

Fleroxacin was given at single doses of 100 mg i.v. or 400 mg orally to 26 subjects with various levels of renal function. The volume of distribution, systemic availability and peak concentration after oral fleroxacin were independent of the glomerular filtration rate. After declining renal but not nonrenal clearance, the total body clearance of fleroxacin declined with decreasing glomerular filtration rate. The N-oxide metabolite exhibited formation-limited kinetics and the N-demethyl metabolite exhibited elimination-limited kinetics. The AUCs of both metabolites increased with declining renal function. In 7 patients on continuous ambulatory peritoneal dialysis the mean dialysate/plasma concentration ratio of fleroxacin increased with increasing dwell time, resulting in 7.8 % recovery of unchanged fleroxacin in peritoneal dialysate. Fleroxacin was well tolerated. (34)

Spontaneous fleroxacin-resistant mutants of E. coli K-12 exhibiting quinolone-resistant replicative DNA biosynthesis were isolated. 4 of 11 mutants also had decreased amounts of OmpF or OmpC porin. None of

the mutants had changes solely in porin proteins. (35)

Fleroxacin, 200 or 400 mg as a single oral dose, was an efficacious therapy for microbiologically proven chancroid in patients who did not have concurrent HIV-1 infection. Among HIV-1-infected men, a single dose of 200 or 400 mg of fleroxacin was inadequate therapy for chancroid. (36)

In a study in 43 female patients undergoing hysterectomy and adnexectomy, tissue samples were obtained 6, 12 and 24 h after oral administration of 600 mg of fleroxacin. Somewhat higher fleroxacin concentrations were detected in ovarian tissue than in myometrium, and in both cases the tissue/plasma concentration ratio exceeded unity. Fleroxacin concentrations in the fallopian tube tissue were close to, or slightly higher than, those measured concomitantly in plasma. These concentration ratios showed no tendency to increase or decrease with time. The compound was well tolerated. (37)

Intravenous fleroxacin administered to 12 patients with serious infections appeared to be effective. Resistance in Pseudomonas strains and Gram-positive cocci may have been related to bacteriological failure and superinfection; further investigations using a larger number of patients are recommended. (39)

In an open, randomized study in 25 patients with enteric fever, it was concluded that a single daily dose of 400 mg fleroxacin for 2 weeks was an effective and tolerable treatment. (40)

In a study to determine concentrations of fleroxacin in human prostatic tissue and fluid after administration of a single 200 mg oral dose, mean prostatic fluid concentrations at 2 and 4 h were 1.02 and 1.12 mcg/ml, respectively. Ratios of prostatic fluid and serum levels (Pf/S) were 0.51 and 0.58, respectively. This concentration was considered high enough to eradicate most pathogens causing bacterial prostatitis. (41)

Fleroxacin was seen to penetrate well into the maxillary sinus mucosa, tonsil, otorrhea and saliva. Based on these findings as well as its MICs against pathogens, fleroxacin was determined effective for the treatment of otorhinolaryngological infections such as otitis media, sinusitis, tonsilitis and pharyngolaryngitis. (42)

In a study in 11 patients, fleroxacin was seen to be effectively concentrated in the bronchoalveolar lining fluid, constituting an important barrier against pulmonary infections. (43)

Two groups of patients received 200 mg and 300 mg of fleroxacin. When serum and bile penetration were evaluated in the 200-mg group, Cmax was 3.30 and 4.42 mcg/ml, respectively, Tmax was 2-4 and 2-6 h, respectively, and t1/2 was 10-12 and about 12 h, respectively. The 300-mg group presented the same tendency. In view of the longer and higher concentration and penetration ratio in bile, the compound is expected to be a promising oral agent for bile tract infections. (44)

Fleroxacin (800 mg o.a.d. orally for 5 days) reached concentrations in urine and bile far exceeding the MICs of most pathogens commonly found in the gastrointestinal tract. (45)

The pharmacokinetics of fleroxacin were not affected by the addition of metronidazole, clindamycin or ornidazole in a study in 10 healthy volunteers. Title compound + clindamycin resulted in an increased SBA against S. aureus. No antagonistic effects against Gram-negative bacteria by the combinations was seen, and no effect on anaerobes could be

proven using the SBA technique. (46)

In a single dose study 123 female patients with uncomplicated urinary tract infection received either 400 mg of fleroxacin or 3 g of amoxicillin orally. Fleroxacin was significantly more effective than amoxicillin. Adverse reactions in the form of gastrointestinal disturbances and vaginal candidiasis were observed in about 20% of patient in both treatment groups. (51)

In a double blind, randomized study 88 female outpatients with acute, uncomplicated cystitis were treated with a single fleroxacin dose of 200 mg or 400 mg. The compound was clinically and bacteriologically effective in most patients. Mild to moderate gastrointestinal and CNS adverse events were seen in 11 patients. (52)

A daily dose of 400 mg fleroxacin appears to be effective for treating uncomplicated urinary tract infections, with a tolerance comparable to other quinolones. (53)

Twelve healthy male volunteers and 13 cystic fibrosis (CF) patients received single (800 mg) and multiple (800 mg/day x 5) doses of fleroxacin. Plasma and urine samples were assayed for unchanged compound and metabolites (N-demethylfleroxacin and N-oxidefleroxacin) by HPLC. After single doses, the former metabolite was renally cleared less rapidly in CF than in volunteers; after multiple doses this effect was seen with the latter metabolite. These variations indicate mechanisms of altered drug excretion in CF. (54)

Pharmacokinetics of fleroxacin and its metabolites are altered in elderly subjects, but these changes are not sufficient to require dose adjustments. (55)

After fleroxacin 400 mg, relatively high plasma levels of 3-6.8 mg/l appeared within 1 h. Elimination half life was 10 h. Within 2-3 days, 59% of the dose was recovered in the urine. Volume of distribution was over 1 l/kg. Total systemic clearance was 135 ml/min and total renal clearance was 76 ml/min. The absolute bioavailability of fleroxacin was close to 100%. Fleroxacin levels in body fluids and tissues exceeded those of plasma. Dose adjustments should be made for subjects with renal clearance below 20-30 ml/min. Due to its good antibacterial and pharmacokinetic properties, a once-daily administration of fleroxacin is justified. (56)

Men and women with suspected or proven Chlamydia trachomatis genital infections were treated with 400, 600 or 800 mg/day fleroxacin for 7 days in a double-blind study. In men monitored for at least 6 weeks or until therapy failure, fleroxacin erradicated C. trachomatis in 5/8 on low dose, 3/4 on middle dose and 3/7 on high dose. All women monitored during this time period became culture-negative. MICs were 4-8 mcg/ml for nearly all isolates tested. In patients with initial positive cultures for Ureaplasma urealyticum, follow-up cultures remained positive in 29% of men and 50% of women. Men with nongonococcal urethritis receiving high-dose fleroxacin showed significantly more frequent clinical response than those treated with lower doses. Adverse events, most often insomnia and photosensitivity reactions, were frequent, dose-related and often severe. The study was terminated prematurely due to side effects and unacceptably high rates of microbiological failure. (65)

Unexpectedly high rates of adverse effects were encountered in a double-blind study of once-daily oral fleroxacin (400, 600 or 800 mg) for 7 days in the treatment of ambulatory patients with uncomplicated

genital infections. Side effects occurred in 66/79 (84%) patients, which were severe in 38 cases (48%) and dose-related in all cases. Most common were CNS reactions (70%), especially insomnia (49%), gastrointestinal reactions (39%) and photosensitivity reactions (10%). The latter were found to correlate with outdoor occupations. No other external factors could be found to correlate with adverse effects. The investigators concluded that 600- and 800-mg single daily doses of fleroxacin caused an unacceptably high rate of adverse effects. (66)

HPLC procedures were developed for the measurement of fleroxacin, temafloxacin and A-64730 in serum, urine and bile. A C18 reversed-phase analytical column with spectrofluorimetric detection was used. At a signal-to-noise ratio of 4, the detection limits in serum were 2.5, 10 and 20 ng for each compound, respectively. The intra- and interassay coefficients of variation were in the ranges of 0.8-5.4 and 2.2-7.6%, respectively. (67)

Fleroxacin and pefloxacin were assayed in a rat abscess model. Peak fleroxacin concentration in the serum of infected animals was 14.6 +/- 4.7 mg/l; peak concentration in the abscess fluid at 24 and 96 h was 12.3 +/- 2.5 and 4.7 +/- 2.6 mg/l. Fleroxacin persisted significantly longer in abscess fluid than in serum. Neither drug sterilized the abscesses following single drug administration, but after multiple administration all abscesses became sterile. It was suggested that fleroxacin may be suitable for treatment of closed-space infections induced by susceptible microorganisms. (68)

Sixty-two patients with complicated UTIs were given once-daily fleroxacin (200, 400 or 600 mg) for 10 days. Therapy was discontinued in 15 patients due to adverse effects and in 2 due to treatment failure. Thirty-five of 45 evaluable patients reached clinical cure. No significant difference was seen between the 3 doses tested. Overall favorable bacteriological response was 80% at 4-6 weeks after therapy . The greatest incidence of adverse effects was seen in the 600-mg group. Thus 200 or 400 mg fleroxacin was suggested to be appropriate for the once-daily treatment of complicated urinary tract infections. (74)

Results from an international multicenter study indicated that single doses of fleroxacin are highly effective in the treatment of bacterial cystitis in women. Single doses of 400 mg fleroxacin or 600 mg trimethoprim were administered to 40 women with urinary tract infections. Sixteen of 17 patients treated with fleroxacin and 16 of 18 on trimethoprim were cured. Side effects were minimal. Fleroxacin demonstrated a longer half-life than new quinolones such as norfloxacin, enoxacin and ciprofloxacin. (75)

In 19 young and 18 elderly volunteers a theophylline plasma concentration of 10 mcg/ml was attained, followed by oral fleroxacin (400 mg once daily) administration. Total theophylline clearance remained essentially unchanged throughout the study period (3.5 and 2.9 l/h in the young and the elderly, respectively), both after single and multiple fleroxacin doses. Although significant changes occurred in the urinary excretion of unchanged theophylline and its metabolites after a single fleroxacin dose, no changes were observed after multiple doses. Adverse reactions consisted mainly of gastrointestinal and sleep disturbances, and were related to theophylline; photosensitivity was observed in 6 subjects and was attributed to fleroxacin. (81)

In 6 patients with skin or skin structure infections who received 400 mg fleroxacin once daily, serum Cmax was 6.2 mcg/ml and Tmax 0.94 h. The absorption t1/2, alpha t1/2, beta t1/2, apparent steady-state Vd, apparent total body Cl and renal Cl were 0.56 h, 0.78 h, 10.56 h, 0.85

l/kg, 129.2 ml/min and 53.3 ml/min, respectively. Fleroxacin disposition in this patient population was similar to that in healthy volunteers. (82)

Nineteen patients with superficial suppurative infections received oral fleroxacin 1 to 3 times daily in single doses of 100-200 mg and up to 300 mg. Duration of treatment varied from 2 to 28 days. Total administered doses varied from 200 to 7500 mg. Response was excellent in 6 patients, remarkable in 9, poor in 2 and no improvement in 2. The bacterial elimination rate was 90.9%. In 4 patients taking a single dose of 200-300 mg, skin tissue concentration of fleroxacin measured after an average of 3.6 h was 1.4- to 1.86-fold the level in serum. (83)

In a double-blind, randomized study in 45 patients with complicated urinary tract infections fleroxacin was given orally at doses of 200, 400 or 600 mg for 10 days. Clinical cure was achieved in 78% of patients. A favorable bacteriological response was obtained in 80% of patients. Relapse occurred in 8 patients and superinfection in 3. No significant difference was found among the 3 dosage groups. During therapy 1 K. ozaenae strain became resistant and 1 P. aeruginosa became less sensitive to fleroxacin. In 13 patients therapy was stopped due to major adverse reactions that included oliguria, psychosis, photosensitivity, insomnia and nausea. Increased dose correlated with number of adverse effects. (84)

A new HPLC chromatographic method for the quantitative determination of fleroxacin and its N-demethyl and N-oxide metabolites in plasma and urine, using internal standards, is described. A mixture of the plasma or urine and a solution of the standard is submitted to an extraction process and quantificated on a reversed-phase Toyo Soda TSK ODS-120T column using 10 mM tetrabutylammonium hydrogen sulfate and 50 mM KH2PO4 in water as mobile phase. A fluorometric detector with excitation and detection wavelengths of 290 and 450 nm, respectively, is used. The practical limit of quantification in plasma is about 10 ng/ml for fleroxacin and for its metabolites, although the fluorescence sensitivity for the latter is lower. The limit in urine is 1 mcg/ml for fleroxacin and 0.5 mcg/ml for its metabolites. The interassay coefficient of variation is 5.5 and 4%, respectively, in plasma and urine. (86)

Twelve elderly patients received a single oral dose of 800 mg fleroxacin. Plasma Cmax was 15.6 mg/l, Tmax was 3 h, t1/2 was 16 h and 39% of the dose was excreted as unchanged compound in urine. Metabolites accounted for 4% of plasma drug concentration. Plasma parameters were mainly correlated with age and weight; urinary parameters were correlated with creatinine clearance. Compared with results in younger subjects, no significant change in the t1/2 of fleroxacin or its metabolites was observed. The apparent volume of distribution was lower in elderly than in younger patients, and a 2-fold decrease in apparent total clearance was noted; plasma concentrations were consequently higher in elderly than in younger patients. (87)

A single oral dose of 400 mg fleroxacin was given to 6 healthy subjects and to 24 patients with renal insufficiency. In healthy subjects, Cmax was 6.8 mg/l, Tmax was 1h, t1/2 was 14 h, total clearance was 4.86 l/h and 48% of unchanged fleroxacin was excreted in urine in 48 h. Plasma metabolites accounted for no more than 5% of the levels of parent compound. In uremic patients Cmax was unchanged, Tmax increased, Vd/f did not change, t1/2 was prolonged and AUC was multiplied by 2 or 3. A linear relationship was found between total and renal clearances of fleroxacin and creatinine clearance. Accumulation of N-demethyl-fleroxacin and N-oxide-fleroxacin was very high in uremic patients. Dialysance of fleroxacin and its metabolites was about 3.6 to 4.8 l/h. (88)

No convulsions were evoked in mice at high oral combination doses of fleroxacin and fenbufen. Brain-to-serum concentration ratios of fleroxacin after oral dosing were 0.13 in mice, 0.19 in rats and 0.28 in dogs. Rats showed no accumulation of fleroxacin in brain and elimination from the brain was similar to that from serum after the oral dose. Dogs exhibited similar drug distribution into various brain regions. The inhibitory effect of fleroxacin on GABA receptor binding was relatively weak but was slightly potentiated in the presence of 4-biphenylacetic acid. Demethyl fleroxacin showed more potent inhibition of GABA receptor binding and potentiation with 4-biphenylacetic acid. Fleroxacin N-oxide showed only slight inhibition of GABA receptor binding, which was not influenced by 4-biphenylacetic acid. (92)

Twelve healthy subjects received 400 mg fleroxacin as a 1-h i.v. dose once daily for 4 days, followed by 400 mg p.o. once daily for 4 days. Steady-state plasma concentrations achieved with the i.v. route were maintained after the switch to the oral route. The mean steady-state pharmacokinetic parameters were similar for both routes. The drug was well tolerated. (93)

In a multicenter study, 74 patients with complicated urinary tract infections (41), skin and soft tissue infections (24) or pneumonia/pneumonitis (9) received fleroxacin (400 mg i.v., once daily). Among patients with UTI, 93% were bacteriologically cured and 97% clinically cured. Among those with SKST, 33% were bacteriologically cured and 58% clinically cured or improved. In the pneumonia group, 55 and 78% were bacteriologically and clinically cured. Bacteriological and clinical failure was seen more frequently in infections due to S. aureus and appeared to be associated with resistance development. Adverse reactions involved the digestive system (27% of patients), being mostly nausea or vomiting, the central nervous system (9%), predominantly headache and insomnia, and the injection site (3%). (95)

In a double-blind, multicenter study in 64 patients with complicated and/or recurrent urinary tract infections, fleroxacin (400 mg p.o., once daily) or norfloxacin (400 mg p.o., b.i.d.) was given for ten days. All patients under fleroxacin and all but one under norfloxacin were bacteriologically cured. Clinical cure rates were 93 and 87% in the fleroxacin and norfloxacin groups, respectively. Adverse reactions appeared in 22% of patients in the fleroxacin group and in 16% in the norfloxacin group, with nausea being reported most frequently in each group. (107)

In a multicenter, double-blind study in 79 patients with complicated urinary tract infections, fleroxacin (400 mg s.i.d.) or norfloxacin (400 mg b.i.d.) was given for a median of 10 days. Success rates for fleroxacin and norfloxacin were 86.7 and 89.7%, respectively. Adverse reactions under fleroxacin were gastrointestinal disturbances in 3 patients, insomnia and nausea in 4 patients and rash in 1 patient. In the norfloxacin group, gastric pain and rash were reported by one patient each. (110)

In a randomized, double-blind study in urethral infections in males and endocervical infections in females caused by Chlamydia trachomatis, 82 patients received fleroxacin (600 mg once a day) or doxycycline (100 mg twice a day). Bacteriologic cure rates were 96% for fleroxacin and 89% for doxycycline. Clinical cure rates were 96% for both compounds. Adverse reactions to fleroxacin included nausea (12%) and vomiting (1 patient). Doxycycline produced vomiting (5%) and an allergic reaction in 1 patient. (114)

In a randomized, double-blind study, 106 patients with skin and soft tissue infections received fleroxacin (400 mg/day p.o.) or augmentin (500/125 mg t.i.d. p.o.), for 4-21 days. S. aureus was the most frequently isolated pathogen. Bacteriologic cure rate was 96% under fleroxacin with 2 superinfections and 87% under augmentin with 1 superinfection. Clinical cures were 75 and 70%, respectively. Both medications were well tolerated. Adverse reactions appeared in 23% in the fleroxacin group and in 25% in the augmentin group. (123)

In a randomized, open study in complicated urinary tract (16 patients) and lower respiratory tract infections (8 patients), fleroxacin (400 mg i.v. once daily) or ceftazidime (2 g b.i.d.) was given for 7 days. The pathogens isolated were S. pneumoniae, B. catarrhalis and Pasteurella in LRTI and E. coli, Proteus sp., Klebsiella sp., Serratia sp., Achromobacter and Aeromonas in UTI. All patients were successfully treated, with the exception of one female patient with UTI due to indwelling catheter. One patient with mild transient exanthema on both legs and one with diarrhea after multiple antibiotic pretreatment were observed in the fleroxacin group. (128)

A new HPLC method for the quantitive determination of fleroxacin in biological fluids, using ciprofloxacin as internal standard, has been presented. The purified plasma extract was injected into a Zorbax ODS column, eluted with 0.025 N H3PO4 (adjusted at pH 2.4 with Bu4NOH) - methanol - acetonitrile, and the quantification performed with a fluorescence detector (excitation at 281 nm; detection at 470 nm). The calibration curves ranged from 0.2 to 20 mcg/ml, and precision was better than 5%. The method showed an RSD = 4.9%, the detection limit being 0.1 mcg/ml. (129)

Patients with biliary tract infections undergoing cholecystectomy received fleroxacin (800 mg/day p.o.) for 5 days. Plasma Cmax was 8.2 mg/l at 8.3 h. The harmonic mean elimination t1/2 was 10.5 h. There was a reduction in renal clearance. Cmax in T-drain bile was 2- to 3-fold greater than in plasma; the individual ratios of bile/plasma AUC ranged from 1.3 to 9.9. Fleroxacin was eliminated mainly by the kidneys. The fraction of the 5th dose eliminated in 24-h urine was reduced, and the fraction of dose in the urine as N-demethyl and N-oxide metabolites was elevated. The MICs for most pathogens causing biliary tract infections were surpassed in plasma and bile for more than 24 h. (133)

A whole issue dealing with in vitro and in vivo antibacterial activity, toxicity, pharmacology , pharmacokinetics and clinical studies of fleroxacin has been published. (136)

In an open study, 27 patients with acute osteomyelitis or septic arthritis received fleroxacin at single oral doses of 400 mg/day for a mean of 44 days. At a 3-month follow-up, 81% of patients with acute osteomyelitis and all patients with septic arthritis were bacteriologically and clinically cured. Eight patients had adverse reactions, mainly dizziness, rash and photosensitivity. (137)

Using positron emission tomography, a randomized, placebo-controlled trial in 18 healthy volunteers demonstrated that short-term fleroxacin has no significant effect on cerebral blood flow, glucose or oxygen metabolism. (149)

Fleroxacin was found to penetrate well into gynecological tissues after a single oral dose (200 mg). Clinical and bacteriological efficacy rates in 113 patients with gynecological infections treated with 200 or 300 mg p.o. once daily for 3-28 days were 97.1 and 89.1%, respectively. Few side effects were reported. (151)

Fleroxacin showed good penetration into skin and blister fluid after a single oral dose (200 mg). Overall clinical efficacy in 49 patients with dermatological infections who were administered 200 or 300 mg once daily for 5-14 days was 81.6%. No side effects were observed. (154)

Experimental and clinical studies showed excellent penetration of fleroxacin into skin. Overall clinical efficacy rate in patients with skin and skin structure infections administered 200 or 300 mg once daily for 3-15 days was 74%. No side effects were observed. (155)

In patients with chronic otitis media, fleroxacin (200 mg p.o.) showed good penetration into otorrhea. At 200 or 300 mg p.o. once daily, it showed good clinical and bacteriological efficacy. (171)

An NDA has been submitted for AM-833 by Kyorin in Japan. (179)

Fleroxacin (300 mg once daily p.o. for 14 days) and ofloxacin (600 mg/day in 3 divided doses p.o. for 14 days) exhibited similar efficacy and safety in a double-blind trial in patients with respiratory tract infections. (180)

Fleroxacin (600 mg once daily for 7 days) and doxycycline (100 mg b.i.d. for 7 days) exhibited similar efficacy in a large double-blind, randomized trial in men and women with uncomplicated chlamydial infection. Incidence of side effects and withdrawal rates due to side effects were higher on fleroxacin. (188)

In 7 lactating women administered a single 400-mg p.o. dose of fleroxacin, plasma pharmacokinetics were similar to those previously reported in volunteers and penetration into breast milk was found to be 65%. (189)

In a double-blind, randomized trial in 556 evaluable women with acute uncomplicated urinary tract infections, fleroxacin 400 mg as single dose showed similar clinical efficacy and safety, but less bacteriological efficacy, compared to fleroxacin 200 mg q.d. for 7 days or ciprofloxacin 250 mg b.i.d. for 7 days. (190)

A rabbit model for ocular pharmacokinetic analysis has been described. Sequential aqueous and vitreous humor and serum samples were obtained after i.v. and intraocular administration of fleroxacin, and mean data from individual animals were combined to give population data. (191)

In a multicenter, open, randomized trial in 26 patients with skin and skin structure infections, i.v. fleroxacin (400 mg once daily) exhibited efficacy and safety similar to i.v. ceftazidime (1 g t.i.d.), with the advantage of once-daily dosing. (192)

An NDA has been submitted for fleroxacin in Japan by Kyorin. In Europe, Roche is finishing phase III trials. (194)

Results from an open-label study indicated that no change in loading dose of fleroxacin is required in patients with compromised liver function, while a 50% decrease in maintenance dose is required only in patients with ascites. (195)

In a trial in 50 male patients with complicated urinary tract infections treated with i.v. fleroxacin (400 mg once daily) followed

by oral drug for at least 7 days, 100% eradication of original pathogens was obtained; however, there was a very high percentage of superinfections with resistant S. aureus (32%). Compound was well tolerated. (199)

A new synthesis of fleroxacin, labeled with fluorine-18, has been described. The reaction of 6,7, 8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester (I) with 2-bromoethanol (II) gives 6, 7,8-trifluoro-1-(2-hydroxyethyl)-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid ethyl ester (III),which is condensed with N-methylpiperazine (IV), yielding 6, 8-difluoro-1-(2-hydroxyethyl)-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester (V). The reaction of (V) with methanesulfonyl chloride affords the corresponding mesylate (VI), which is treated with (18F)-KF in dichloromethane at 80 to give 6, 8-difluoro-1-(2-fluoroethyl)-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester (VII). Finally this compound is hydrolyzed with NaOH. (203)

The proceedings of a symposium on fleroxacin have been published. (214)

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